Mol Divers (2010) 14:443–453
DOI 10.1007/s11030-009-9223-z

FULL-LENGTH PAPER

Three-component synthesis of benzo[b][1,5]thiazepines via coupling–addition–cyclocondensation sequence

Benjamin Willy · Thomas J. J. Müller

Received: 18 August 2009 / Accepted: 27 December 2009 / Published online: 16 February 2010

Abstract 2,4-Disubstituted benzo[b][1,5]thiazepines represent nonfluorescent intense yellow chromophores and are readily synthesized from acid chlorides, terminal alkynes, and *ortho*-amino thiophenols by a consecutive one-pot three-component Sonogashira coupling–Michael addition–cyclocondensation sequence under mild conditions in good yields.

Keywords Benzothiazepines · C–C coupling · Cyclocondensation · Microwave reaction · MCR

Introduction

The 1,5-benzothiazepine framework has been identified as a pluripotent pharmacophore with derivatives encompassing CNS-acting agents, anti-HIV and anticancer drugs, angiotensin converting enzyme inhibitors, antimicrobial and antifungal compounds, calmodulin antagonists, bradykinin receptor agonists, as well as Ca^{2+} blockers (Fig. 1) [1]. In addition, dihydro 1,5-benzothiazepines have become increasingly interesting since many derivatives exhibit antifungal, anti-bacterial [2–4], anti-feedant [5], anti-inflammatory, analgesic [6], and anti-convulsant [7] activity. Likewise, the related 1,5-benzothiazepines display a comparable spectrum of biological activity [8,9].

Syntheses of 1,5-benzothiazepines can be achieved through various routes starting from 2-aminothiophenol and 1,3-difunctional three-carbon building blocks [10,11]. Among them, α, β-unsaturated carbonyl compounds such as enones [12–18] and ynones [19–24] are suited best for Michael addition and subsequent cyclocondensation. Albeit benzothiazepines possess highly interesting pharmaceutical properties, a diversity-oriented synthesis [25–28,30,31] approach using the advantages of multi-component reactions [32–42] has remained unexplored to date. As part of our program directed to the design of new multi-component syntheses of pharmaceutically and electronically interesting heterocycles [25,26] initiated via Sonogashira cross coupling [43–46], we have focused on a cross coupling–cyclocondensation approach. Here, we report on a concise, consecutive one-pot three-component synthesis of benzo[b][1,5]thiazepines with a flexible substitution pattern and their UV/vis absorption properties as a consequence of the extended π-electron conjugation.

B. Willy · T. J. J. Müller (✉)
Institut für Organische Chemie und Makromolekulare Chemie, Heinrich-Heine-Universität Düsseldorf, Universitätsstraße 1, 40225 Düsseldorf, Germany
e-mail: ThomasJJ.Mueller@uni-duesseldorf.de

Results and discussion

Alkynones are easily accessible via the Sonogashira coupling [47–53] of acid chlorides with terminal alkynes [54]. In contrast to the literature-known syntheses, we have reported a variation in THF as a solvent where only one equivalent of triethylamine as a base is needed to achieve an efficient alkynone synthesis [55,56]. The alkynone formation is sufficiently mild and complete conversion at ambient temperature within less than an hour was established as a catalytic entry to ynones for consecutive heterocycle synthesis. The resulting alkynones are reactive toward cyclocondensation with binucleophiles, such as hydrazines furnishing pyrazoles [57], amidines furnishing pyrimidines [55,58–60], and *ortho*-phenylene diamines furnishing benzodiazepines [61] in a one-pot fashion. This concept should also be transposable to the MCR synthesis of benzothiazepines. Hence, the final Michael addition–cyclocondensation step had to be optimized.

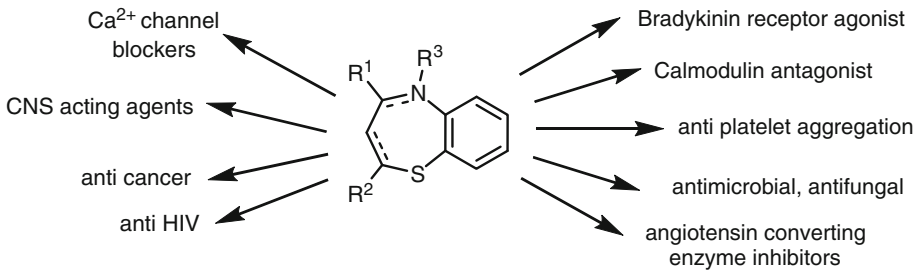
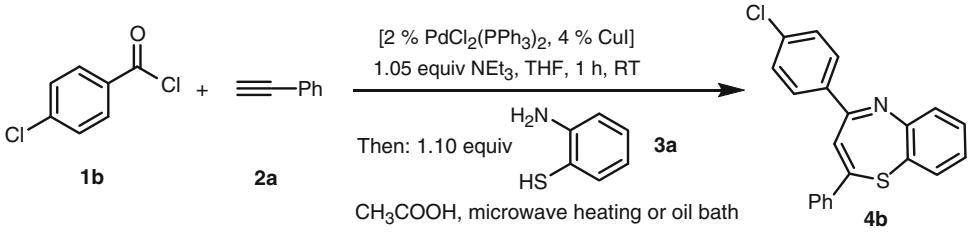


Fig. 1 The 1,5-benzothiazepine framework



Scheme 1 Optimization of the cyclocondensation step in the three-component synthesis of benzo[b][1,5]thiazepine **4b**

Table 1 Optimization of the cyclocondensation step in the coupling–addition–cyclocondensation synthesis of 2,4-disubstituted benzo[b][1,5]thiazepine **4b** starting from acid chloride **1a**, alkyne **2a**, and *ortho*-amino thiophenol (**3a**)[a]

Entry	Temperature (°C)	Time (min)	Yield (%)
1	90	60	79
2	120	60	75
3	60	60	81
4	60	30	80
5	60	10	80
6[b]	60	60	37

[a] Reaction conditions 1.00 equiv. of acid chloride **1a**, 1.00 equiv. of alkyne **2a** (0.25 M in THF), 1.05 equiv. of NEt_3, 0.02 equiv. of $PdCl_2(PPh_3)_2$, 0.04 equiv. of CuI, were successively reacted for 1 h at rt. and then 1.10 equiv. of *ortho*-amino thiophenol (**3a**) and 20 equiv. of acetic acid were added and the reaction mixture was heated in the microwave cavity under conditions indicated

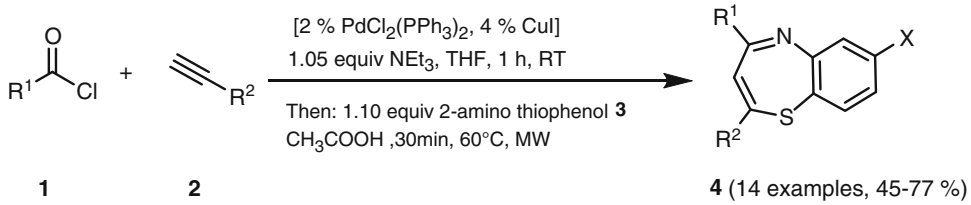
[b] The cyclocondensation step was performed under conductive heating in an oil bath

As model reaction *p*-chlorobenzoyl chloride (**1b**) and phenyl acetylene (**2a**) were first reacted under Sonogashira conditions for 1 h at room temperature to furnish the expected alkynone, and after the subsequent addition of 2-aminothiophenol (**3a**) and acetic acid upon varying reaction temperature upon irradiation with microwaves and time led to the formation of benzothiazepine **4b** (Scheme 1; Table 1).

The optimization of the concluding heterocyclization clearly showed that dielectric heating is superior over conductive heating (entries 3 and 6). In comparison to the MCR synthesis of benzo[b][1,5]diazepines [60] this result is just converse. Although the Michael addition and cyclocondensation are essentially completed after 10 min at 60 °C in the microwave cavity (entries 3–5) for electronically diverse substitution, a reaction time of 30 min at 60 °C was chosen as the optimal condition (entry 4). With these optimization in hand a series of acid chlorides **1**, alkynes **2**, and the *ortho*-aminothiophenols **3a** and **3b** were submitted to the coupling–addition–cyclocondensation sequence to give various 2,4-disubstituted benzo[b][1,5]thiazepines **4** as yellow to brown or red solids or resins in moderate to good yields (Scheme 2; Table 2).

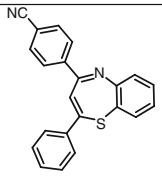
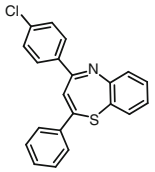
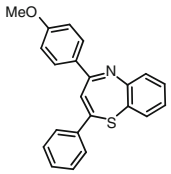
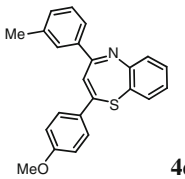
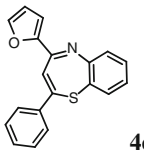
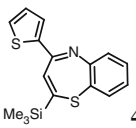
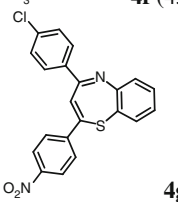
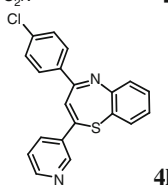
The structures of 2,4-disubstituted benzo[b][1,5]thiazepines **4** were unambiguously supported by spectroscopic (^1H, ^{13}C and DEPT NMR experiments, IR, UV–vis, mass spectrometry), and elemental analyses. Most characteristically for the successful heterocyclization is the appearance of the central methine proton singlets between δ 6.9 and 7.4 in the proton NMR spectra.

Interestingly, the molecular mass of the benzothiazepines could only be detected by MALDI–TOF spectrometry with dithranol (DIT) and 2-[(2*E*)-3-(4-*t*butylphenyl)-2-methylprop-2-enyliden]malononitrile (DCTB) as a matrix. In the EI experiments the signals could always be assigned to quinolines arising from sulfur extrusion.



Scheme 2 One-pot three-component synthesis of 2,4-disubstituted benzo[b][1,5]thiazepines **4**

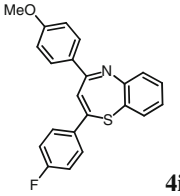
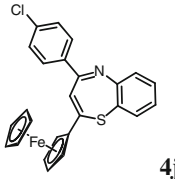
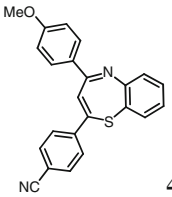
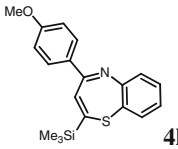
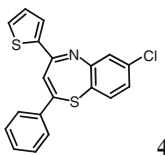
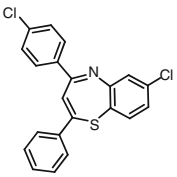
Table 2 One-pot three-component coupling–addition–cyclocondensation synthesis of 2,4-disubstituted benzo[b][1,5]thiazepines **4**

Entry	Acid chloride **1**	Alkyne **2**	*ortho*-Amino thiophenol **3**	Benzothiazepine **4**
1	**1a**: R^1 = 4-CN-C_6H_4	**2a**: R^2 = C_6H_5	**3a**: X = H	 **4a** (68 %)
2	**1b**: R^1 = 4-Cl-C_6H_4	**2a**	**3a**	 **4b** (73 %)
3	**1c**: R^1 = 4-OMe-C_6H_4	**2a**	**3a**	 **4c** (65 %)
4	**1d**: R^1 = 3-Me-C_6H_4	**2b**: R^2 = 4-OMe-C_6H_4	**3a**	 **4d** (77 %)
5	**1e**: R^1 = 2-furyl	**2a**	**3a**	 **4e** (60 %)
6	**1f**: R^1 = 2-thienyl	**2c**: R^2 = $SiMe_3$	**3a**	 **4f** (45 %)
7	**1b**	**2d**: R^2 = 4-NO_2-C_6H_4	**3a**	 **4g** (65 %)
8	**1b**	**2e**: R^2 = 3-pyridyl	**3a**	 **4h** (57 %)

In the UV/Vis spectra of 2,4-disubstituted benzo[b][1,5] thiazepines **4** three distinct absorption maxima are found at 254–276 nm, 280–329 nm, and 341–390 nm (Table 3). In the case of the ferrocenyl-substituted derivative **4j** an additional longest wavelength absorption band is found at 486 nm arising from a metal-to-ligand charge transfer. Interestingly and in contrast to the related benzo[b][1,5]diazepines [61], all chromophores **4** are nonfluorescent upon excitation at 280–380 nm.

The donor–acceptor or push–pull substituted derivative **4k** was chosen as a model of this class of extended π-electron systems for the assignment of the absorption bands in the electronic spectra. First, the geometry optimization was computed on the AM1 level of theory [62].

Table 2 continued

Entry	Acid chloride **1**	Alkyne **2**	*ortho*-Amino thiophenol **3**	Benzothiazepine **4**
9	**1c**	**2f**: R^2 = 4-F-C_6H_4	**3a**	 **4i** (68 %)
10	**1b**	**2g**: R^2 = ferrocenyl	**3a**	 **4j** (57 %)
11	**1c**	**2h**: R^2 = 4-CN-C_6H_4	**3a**	 **4k** (59 %)
12	**1c**	**2c**	**3a**	 **4l** (48 %)
13	**1f**	**2a**	**3b**: X = Cl	 **4m** (61 %)
14	**1b**	**2a**	**3b**	 **4n** (61 %)

Based on the AM1 structure optimization of **4k** single-point ZINDO-CI calculations [63–67] were performed to assign the electronic structure of the longest wavelength absorption bands [68]. The three longest wavelength bands of **4k** at 274, 299, and 380 nm are reproduced by the calculations with absorption bands at 269, 295, and 341 nm. The lowest energy band at 341 nm, i.e. the S_1 state, displays considerable oscillator strength and consists to 47% of a HOMO–LUMO transition, wherein the sense of a π–π^* transition electron density is transferred from the central seven-membered benzothiazepine core (HOMO) to the *p*-cyanophenyl substituent and the benzothiazepine (LUMO) (Fig. 2). Besides FMO transitions from HOMO to LUMO+1 (16%) and HOMO-2 to LUMO (5%), transitions from HOMO-7 to LUMO (9%) and HOMO-7 to LUMO+1 (8%) can also contribute to the S_1 state. The band at 295 nm has a similar oscillator strength and is based on the S_2 singlet state, where substantial contributions of HOMO–LUMO (23%), HOMO-1–LUMO (22%), HOMO-2–LUMO (7%), HOMO-7–LUMO (12%), and HOMO-7–LUMO+1 (10%) are found. The S_6 singlet state displays the highest oscillator strength and arises from the absorption band at 269 nm. It consists of HOMO–LUMO+1 (56%), HOMO-1–LUMO (12%), HOMO-2–LUMO (5%), and HOMO-2–LUMO+1 (7%) transitions. The intensity of all three bands can be rationalized qualitatively by consulting the orbital coefficients of the three highest occupied frontier molecular orbitals (FMOs) (Fig. 2).

Conclusion

In conclusion, we have established a versatile one-pot three-component synthesis of 2,4-disubstituted benzo[b]

Table 3 UV/Vis data of 2,4-disubstituted benzo[b][1,5]thiazepines **4** (recorded in CH_2Cl_2, $c_0 = 10^4$ M, $T = 293$K)

Compound	$\lambda_{max}(\varepsilon)$ (nm) ($mol^{-1}Lcm^{-1}$)
4a	274 (39200), 320 (10000), 390 (2200)
4b	270 (32900), 308 (12800), 329 (9700), 359 (3000)
4c	276 (26800), 308 (19000), 380 (3000)
4d	264 (33000), 280 (22800), 320 (12500), 341 (8000)
4e	273 (27700), 310 (18500), 381 (4600)
4f	262 (13200), 309 (9700), 386 (1900)
4g	254 (19700), 285 (22300), 370 (4600)
4h	270 (26700), 380 (2400)
4i	273 (21900), 305 (17200), 370 (4000)
4j	262 (24600), 281 (26800), 380 (3500), 486 (1500)
4k	274 (30200), 299 (22500), 380 (3200)
4l	260 (8000), 297 (10300), 380 (2000)
4m	274 (23600), 310 (15000), 390 (2900)
4n	270 (28600), 308 (13900), 329 (11100), 348 (4200)

[1,5]thiazepines via a consecutive coupling–addition–cyclocondensation sequence assisted by microwave irradiation for the final addition–cyclocondensation step. The electronic spectra of these yellow chromophores can be interpreted by ZINDO-CI calculations. In contrast to 2,4-disubstituted benzo[b][1,5]diazepines [61] the title compounds are essentially nonfluorescent. Studies expanding this novel modular approach to enhance molecular diversity in targets which are of special interest to pharmaceutical applications are currently underway.

Experimental section

General considerations

All reactions involving water-sensitive compounds were carried out in flame-dried glassware under argon atmosphere. Reagents and catalysts were purchased reagent grade and used without further purification. Solvents were dried by a solvent purification system. Flash column chromatography: silica gel 60, mesh 230–400. TLC: silica gel plates ($60F_{254}$). ^{1}H−, ^{13}C−, DEPT-, NOESY-, COSY-, HMQC-, and HMBC spectra were recorded on a 500-MHz NMR spectrometer (Bruker Avance Dex 500) using $CDCl_3$ as solvent (tetramethylsilane as an internal standard). The assignments of quaternary C_{quat}, CH, CH_2, and CH_3 were made on the basis of DEPT spectra. Mass spectra were recorded on a quadruple spectrometer (Bruker Ultraflex TOF). The melting points are uncorrected (Reichert Thermovar). Elemental analyses were carried out in the microanalytical laboratory of the Pharmaceutical Institute of the Heinrich-Heine-Universität Düsseldorf. Dielectric heating was performed in a single-mode microwave cavity (Discover Labmate, CEM) producing continuous irradiation at 2,450 MHz.

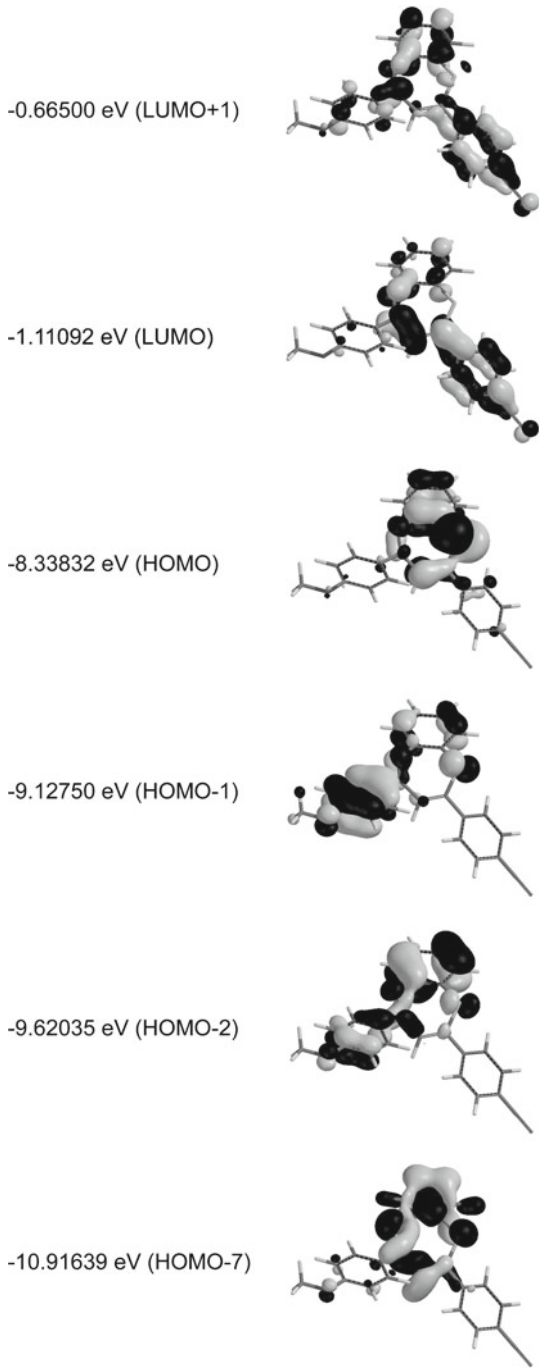


Fig. 2 Selected frontier molecular orbitals (FMOs) and orbital energies of **4k**

General procedure for the one-pot three-component syntheses of 2,4-disubstituted benzo[b][1,5]thiazepines **4**

In a 10-mL microwave vessel, $PdCl_2(PPh_3)_2$ (15 mg, 0.02 mmol) and CuI (8 mg, 0.04 mmol) were dissolved in

degassed THF (4 mL). Acyl chloride **1** (1.00 mmol), alkyne **2** (1.00 mmol), and triethylamine (1.05 mmol) were then added to this orange solution. The reaction mixture was stirred at room temperature for 1 h. Finally, the 2-aminothiophenol **3** (1.10 mmol), followed by glacial acetic acid (1 mL), were added to this suspension, and the reaction mixture was irradiated with microwaves at 60 °C in the microwave reaction chamber for 30 min. After the system cooled to room temperature, the solvent was removed under reduced pressure, and the crude residue was purified by flash chromatography on (silica gel, hexane/ethyl acetate) to afford the analytically pure benzo[b][1,5]thiazepines **4**.

*4-(2-Phenylbenzo[b][1,5]thiazepin-4-yl)benzonitrile (**4a**)*

Following the general-procedure **4a** was obtained as a yellow oil (for details see Table 4). ^{1}H-NMR (500 MHz, acetone-d$_6$): δ 7.20 (s, 1H), 7.30–7.33 (m, 1H), 7.42–7.50 (m, 5H), 7.59 (dd, ^3J = 7.8 Hz, ^4J = 1.2 Hz, 1H), 7.93 (d, ^3J = 8.7 Hz, 2H), 7.98–8.00 (m, 2H), 8.31 (d, ^3J = 8.7 Hz, 2H). ^{13}C-NMR (125 MHz, acetone-d$_6$): δ 115.9 (C$_{quat}$), 120.1 (CH), 125.9 (CH), 128.3 (CH), 129.3 (C$_{quat}$), 129.5 (2CH), 130.4 (2CH), 130.6 (2CH), 131.6 (CH), 131.8 (CH), 134.2 (2CH), 134.4 (C$_{quat}$), 134.6 (CH), 139.9 (C$_{quat}$), 144.8 (C$_{quat}$), 151.8 (C$_{quat}$), 152.4 (C$_{quat}$), 166.0 (C$_{quat}$). MALDI–TOF (DIT, CHCl$_3$, *m/z*): 339 ([M + H]$^+$), 307 ([M – S]$^+$). IR (KBr): $\tilde{\nu}$ = 2224 cm^{-1} (s), 1590 (s), 1560 (s), 1543 (s), 1509 (w), 1491 (s), 1459 (m), 1317 (m), 1205 (m), 1090 (m), 1036 (m), 848 (s), 762 (s), 730 (w), 694 (m), 557 (m), 535 (w). Anal. calcd. for C$_{22}$H$_{14}$N$_2$S (338.4): C 78.08, H 4.17, N 8.28; Found: C 78.57, H 4.14, N 7.74.

*4-(4-Chlorophenyl)-2-phenylbenzo[b][1,5]thiazepine (**4b**)*

Following the general procedure **4b** was obtained as a brown solid, mp 76 °C (for details see Table 4). ^{1}H-NMR (500 MHz, acetone-d$_6$): δ 7.14 (s, 1H), 7.44–7.45 (m, 2H), 7.52–7.64 (m, 6H), 8.00 (s, 1H), 8.14 (d, ^3J = 8.7 Hz, 2H), 8.39 (d, ^3J = 8.7 Hz, 2H). ^{13}C-NMR (125 MHz, acetone-d$_6$): δ 120.3 (CH), 127.3 (CH), 128.6 (CH), 129.4 (CH), 130.5 (2CH), 130.0 (CH), 130.6 (2CH), 130.9 (2CH), 131.5 (2CH), 134.5 (CH), 137.0 (C$_{quat}$), 139.8 (C$_{quat}$), 139.9 (C$_{quat}$), 150.5 (C$_{quat}$), 151.2 (C$_{quat}$), 151.7 (C$_{quat}$), 166.2 (C$_{quat}$). MALDI–TOF (DIT, CHCl$_3$, *m/z*): 348 ([M + H]$^+$), 316 ([M – S]$^+$). IR (KBr): $\tilde{\nu}$ = 1638 cm^{-1} (m), 1592 (s), 1561 (m), 1544 (m), 1509 (w), 1487 (s), 1443 (w), 1417 (w), 1355 (w), 1315 (w), 1204 (w), 1175 (w), 1092 (s), 1011 (m), 886 (w), 864 (w), 831 (m), 812 (m), 757 (s), 692 (s), 618 (w), 582 (w), 539 (w). Anal. calcd. for C$_{21}$H$_{14}$ ClNS (347.9): C 72.51, H 4.06, N 4.03; Found: C 72.77, H 4.07, N 3.94.

*4-(4-Methoxyphenyl)-2-phenylbenzo[b][1,5]thiazepine (**4c**)*

Following the general procedure **4c** was obtained as a yellow resin (for details see Table 4). ^{1}H-NMR (500 MHz, acetone-d$_6$): δ 3.87 (s, 3H), 7.05 (d, ^3J = 8.9 Hz, 2H), 7.11 (s, 1H), 7.20–7.23 (m, 1H), 7.41–7.44 (m, 3H), 7.51–7.52 (m, 1H), 7.60–7.61 (m, 1H), 7.75–7.77 (m, 1H), 7.95–7.97 (m, 2H), 8.08–8.10 (m, 2H). ^{13}C-NMR (125 MHz, acetone-d$_6$): δ 56.8 (CH$_3$), 115.6 (2CH), 115.9 (CH), 126.6 (CH), 127.9 (CH), 128.0 (CH), 129.3 (2CH), 130.5 (2CH), 131.3 (2CH), 131.37 (CH), 131.41 (C$_{quat}$), 134.4 (CH), 134.7 (C$_{quat}$), 140.2 (C$_{quat}$), 150.6 (C$_{quat}$), 152.3 (C$_{quat}$), 164.0 (C$_{quat}$), 166.5 (C$_{quat}$). MALDI–TOF (DIT, *m/z*): 344 ([M + H]$^+$), 312 ([M – S]$^+$). IR (film): $\tilde{\nu}$ = 2958 cm^{-1} (s), 2885 (s), 1637 (w), 1601 (m), 1511 (w), 1459 (w), 1442 (w), 1365 (w), 1342 (w), 1318 (w), 1188 (m), 1113 (m), 1069 (s), 1036 (s), 957 (s), 850 (s), 765 (w), 700 (w), 584 (w). Anal. calcd. for C$_{22}$H$_{17}$NOS · 1/5C$_4$H$_8$O$_2$ (343.4 + 17.6): C 75.84, H 5.19, N 3.88; Found: C 75.36, H 5.10, N 3.48.

*2-(4-Methoxyphenyl)-4-m-tolylbenzo[b][1,5]thiazepine (**4d**)*

Following the general procedure **4d** was obtained as a yellow resin (for details see Table 4). ^{1}H-NMR (500 MHz, acetone-d$_6$): δ 2.34 (s, 3H), 3.83 (s, 3H), 6.94 (d, ^3J = 8.8 Hz, 2H), 7.13 (s, 1H), 7.17–7.29 (m, 6H), 7.38–7.41 (m, 2H), 7.66 (s, 1H), 7.78–7.80 (m, 1H). ^{13}C-NMR (125 MHz, acetone-d$_6$): δ 21.3 (CH$_3$), 55.8 (CH$_3$), 114.2 (2CH), 120.1 (CH), 124.0 (C$_{quat}$), 126.2 (CH), 128.4 (C$_{quat}$), 128.5 (CH), 128.7 (CH), 129.1 (2 CH), 129.3 (CH), 129.4 (CH), 130.2 (CH), 130.5 (CH), 131.3 (CH), 133.0 (C$_{quat}$), 138.2 (CH), 138.5 (C$_{quat}$), 159.8 (C$_{quat}$), 162.5 (C$_{quat}$), 164.6 (C$_{quat}$). MALDI-TOF (DIT, CHCl$_3$, *m/z*): 358 ([M + H]$^+$), 326 ([M – S]$^+$). IR (KBr): $\tilde{\nu}$ = 3055 cm^{-1} (w), 2930 (w), 2834 (w), 1608 (s), 1590 (s), 1546 (m), 1502 (s), 1459 (m), 1439 (m), 1401 (w), 1357 (w), 1292 (m), 1247 (s), 1173 (s), 1108 (w), 1032 (s), 881 (w), 833 (s), 813 (w), 786 (w), 764 (m), 706 (m), 656 (w), 639 (w), 627 (w), 584 (w), 560 (w), 516 (w). Anal. calcd. for C$_{23}$H$_{19}$NOS (357.5): C 77.28, H 5.36, N 3.92; Found: C 77.57, H 5.14, N 3.74.

*4-(Furan-2-yl)-2-phenylbenzo[b][1,5]thiazepine (**4e**)*

Following the general procedure **4e** was obtained as a yellow solid, mp 120 °C (for details see Table 4). ^{1}H-NMR (500 MHz, acetone-d$_6$): δ 7.18–7.21 (m, 1H), 7.28–7.30 (m, 3H), 7.44–7.46 (m, 3H), 7.67 (d, ^3J = 8.1 Hz, 1H), 7.78–7.79 (m, 2H), 7.81–7.83 (m, 1H), 8.10–8.13 (m, 2H). ^{13}C-NMR (125 MHz, acetone-d$_6$): δ 124.8 (CH), 126.5 (CH), 127.4 (CH), 128.7 (2 CH$_2$), 129.0 (CH), 129.1 (CH), 129.7 (2CH), 131.0 (CH), 131.2 (CH), 131.5 (CH), 133.3 (C$_{quat}$), 134.9 (CH), 135.8 (C$_{quat}$), 138.9 (C$_{quat}$), 146.5 (C$_{quat}$), 151.0

Table 4 Details of the synthesis of 2,4-disubstituted benzo[b][1,5]thiazepines **4**

Entry	Acid chloride **1**	Alkyne **2**	*ortho*-Amino thiophenol **3**	Benzothiazepine **4**
1	165 mg (1.00 mmol) of **1a**	103 mg (1.00 mmol) of **2a**	138 mg (1.10 mmol) of **3a**	229 mg (68%) of **4a**
2	176 mg (1.00 mmol) of **1b**	103 mg (1.00 mmol) of **2a**	138 mg (1.10 mmol) of **3a**	248 mg (73%) of **4b**
3	171 mg (1.00 mmol) of **1c**	103 mg (1.00 mmol) of **2a**	138 mg (1.10 mmol) of **3a**	226 mg (65%) of **4c**
4	155 mg (1.00 mmol) of **1d**	133 mg (1.00 mmol) of **2b**	138 mg (1.10 mmol) of **3a**	274 mg (77%) of **4d**
	131 mg (1.00 mmol) of **1e**	103 mg (1.00 mmol) of **2a**	138 mg (1.10 mmol) of **3a**	181 mg (60%) of **4e**
5	147 mg (1.00 mmol) of **1f**	99 mg (1.00 mmol) of **2c**	138 mg (1.10 mmol) of **3a**	143 mg (45%) of **4f**
6	176 mg (1.00 mmol) of **1b**	148 mg (1.00 mmol) of **2d**	138 mg (1.10 mmol) of **3a**	212 mg (65%) of **4g**
7	176 mg (1.00 mmol) of **1b**	104 mg (1.00 mmol) of **2e**	138 mg (1.10 mmol) of **3a**	199 mg (57%) of **4h**
8	171 mg (1.00 mmol) of **1c**	121 mg (1.00 mmol) of **2f**	138 mg (1.10 mmol) of **3a**	246 mg (68%) of **4i**
9	176 mg (1.00 mmol) of **1b**	211 mg (1.00 mmol) of **2g**	138 mg (1.10 mmol) of **3a**	262 mg (57%) of **4j**
10	171 mg (1.00 mmol) of **1c**	128 mg (1.00 mmol) of **2h**	138 mg (1.10 mmol) of **3a**	210 mg (59%) of **4k**
11	171 mg (1.00 mmol) of **1c**	99 mg (1.00 mmol) of **2c**	138 mg (1.10 mmol) of **3a**	152 mg (48%) of **4l**
12	147 mg (1.00 mmol) of **1b**	103 mg (1.00 mmol) of **2a**	175 mg (1.10 mmol) of **3b**	221 mg (61%) of **4m**
13	176 mg (1.00 mmol) of **1f**	103 mg (1.00 mmol) of **2a**	175 mg (1.10 mmol) of **3b**	233 mg (61%) of **4n**

(C_{quat}), 164.3 (C_{quat}). MALDI–TOF (DIT, $CHCl_3$, *m/z*): 304 ($[M + H]^+$), 272 ($[M - S]^+$). IR (KBr): $\tilde{\nu} = 3050\,cm^{-1}$ (w), 1603 (s), 1574 (m), 1551 (s), 1491 (w), 1470 (s), 1456 (s), 1317 (m), 1252 (w), 1236 (w), 1202 (w), 1155 (w), 1091 (w), 1068 (w), 1049 (w), 1019 (m), 956 (w), 908 (w), 883 (w), 856 (w), 830 (w), 800 (w), 755 (s), 689 (m), 594 (m), 555 (w). Anal. calcd. for $C_{19}H_{13}$ NOS (303.4): C 75.22, H 4.32, N 4.62; Found: C 75.12, H 4.34, N 4.54.

*4-(Thien-2-yl)-2-(trimethylsilyl)benzo[b][1,5] thiazepine (***4f***)*

Following the general procedure **4f** was obtained as a yellow solid, mp 123 °C (for details see Table 4). ^{1}H-NMR (500 MHz, acetone-d_6): δ 0.26 (s, 9H), 7.04 (s, 1H), 7.15 (dd, $^3J = 5.1$ Hz, $^3J = 3.7$ Hz, 1H), 7.19 (dt, $^3J = 7.5$ Hz, $^4J = 1.4$ Hz, 1H), 7.24 (dd, $^3J = 7.9$ Hz, $^4J = 1.4$ Hz, 1H), 7.31 (dd, $^3J = 7.8$ Hz, $^4J = 1.4$ Hz, 1H), 7.36–7.40 (m, 1H), 7.54 (dd, $^3J = 3.7$ Hz, $^4J = 1.0$ Hz, 1H), 7.69 (dd, $^3J = 5.1$ Hz, $^4J = 1.0$ Hz, 1H). ^{13}C-NMR (125 MHz, acetone-d_6): δ –2.15 ($3CH_3$), 127.2 (CH), 127.7 (CH), 128.9 (CH), 130.1 (C_{quat}), 130.2 (2CH), 131.7 (CH), 133.0 (CH), 136.5 (CH), 146.7 (C_{quat}), 151.1 (C_{quat}), 160.0 (C_{quat}), 162.4 (C_{quat}). MALDI–TOF (DIT, $CHCl_3$, *m/z*): 316 ($[M + H]^+$). IR (KBr): $\tilde{\nu} = 3104$ cm^1 (w), 2954 (m), 1625 (w), 1586 (s), 1560 (s), 1454 (m), 1421 (s), 1354 (w), 1421 (s), 1354 (w), 1297 (m), 1238 (s), 1202 (m), 1154 (w), 1297 (m), 1238 (s), 1202 (m), 1154 (w), 1084 (w), 1056 (m), 980 (w), 952 (s), 857 (s), 834 (s), 786 (m), 752 (s), 718 (s), 627 (w), 573 (w), 521 (w). Anal. calcd. for $C_{16}H_{17}NS_2Si$ (315.5): C 60.90, H 5.43, N 4.44; Found: C 60.81, H 5.42, N 4.16.

*4-(4-Chlorophenyl)-2-(4-nitrophenyl)benzo[b][1,5] thiazepine (***4g***)*

Following the general procedure **4g** was obtained as a yellow solid, mp 159 °C (for details see Table 4). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.31–7.34 (m, 1H), 7.40 (s, 1H), 7.43–7.45 (m, 1H), 7.49–7.52 (m, 1H), 7.56–7.61 (m, 3H), 8.18 (d, $^3J = 8.8$ Hz, 2H), 8.27 (d, $^3J = 9.1$ Hz, 2H), 8.31 (d, $^3J = 9.1$ Hz, 2H). ^{13}C-NMR (125 MHz, acetone-d_6): δ 125.6 (2CH), 128.3 (CH), 128.8 (C_{quat}), 129.2 (CH), 129.6 (CH), 130.6 (2CH), 130.7 (2CH), 131.4 (2CH), 131.8 (CH), 132.2 (C_{quat}), 134.6 (CH), 139.9 (C_{quat}), 146.1 (C_{quat}), 148.9 (C_{quat}), 151.7 (C_{quat}), 158.0 (C_{quat}), 158.3 (C_{quat}). MALDI–TOF (DIT, $CHCl_3$, *m/z*): 393 ($[M + H]^+$), 361 ($[M - S]^+$). IR (KBr): $\tilde{\nu} = 1593$ cm^{-1} (s), 1557 (w), 1510 (s), 1486 (w), 1456 (w), 1434 (w), 1399 (w), 1352 (s), 1324 (s), 1249 (w), 1206 (w), 1177 (w), 1010 (w), 1091 (m), 1009 (m), 946 (w), 858 (m), 833 (m), 822 (m), 808 (m), 765 (m), 752 (m), 735 (w), 709 (w), 690 (w), 599 (w). Anal. calcd. for $C_{21}H_{13}ClN_2O_2S$ (392.9): C 64.20, H 3.34, N 7.13; Found: C 64.07, H 3.29, N 6.97.

*4-(4-Chlorophenyl)-2-(pyrid-3-yl)benzo[b][1,5] thiazepine (***4h***)*

Following the general procedure **4h** was obtained as a yellow solid, mp 131 °C (for details see Table 4). ^{1}H-NMR (500 MHz, acetone-d_6): δ 7.27–7.32 (m, 2H), 7.40–7.50 (m, 3H), 7.55–7.60 (m, 3H), 8.18 (d, $^3J = 8.7$ Hz, 2H), 8.32–8.33 (m, 1H), 8.61 (d, $^3J = 4.7$ Hz, 2H). ^{13}C-NMR (125 MHz, acetone-d_6): δ 124.3 (CH), 126.8 (CH), 127.3 (CH), 128.1 (CH), 128.2 (C_{quat}), 129.6 (2CH), 130.5 (2CH), 130.7 (CH), 133.7 (CH), 135.0 (C_{quat}), 135.8 (CH), 137.6 (C_{quat}), 138.5 (C_{quat}),

147.7 (C_{quat}), 149.5 (CH), 150.9 (C_{quat}), 151.4 (CH), 165.9 (C_{quat}). MALDI–TOF (DIT, $CHCl_3$, *m/z*): 349 ($[M + H]^+$). IR (KBr): $\tilde{\nu}$ = 3052 cm^{-1} (m), 1607 (m), 1592 (m), 1560 (s), 1476 (m), 1398 (s), 1210 (m), 1190 (m), 1170 (w), 1126 (w), 1089 (s), 1024 (w), 1009 (m), 959 (w), 939 (m), 843 (s), 806 (s), 753 (s), 729 (m), 708 (s), 655 (w), 621 (w), 593 (w), 564 (w), 546 (w). Anal. calcd. for $C_{20}H_{13}ClN_2S$ (348.9): C 68.86, H 3.76, N 8.03; Found: C 68.64, H 3.67, N 7.99.

*4-(4-Fluorophenyl)-2-(4-methoxyphenyl)benzo[b][1,5] thiazepine (***4i***)*

Following the general procedure **4i** was obtained as a yellow solid, mp 81 °C (for details see Table 4). ^{1}H-NMR (500 MHz, acetone-d_6): δ 3.87 (s, 3H), 7.04 (d, ^3J = 8.9 Hz, 2H), 7.07 (s, 1H), 7.18–7.23 (m, 3H), 7.34–7.36 (m, 1H), 7.40–7.43 (m, 1H), 7.49–7.51 (m, 1H), 7.99–8.02 (m, 2H), 8.08 (d, ^3J = 8.9 Hz, 2H). ^{13}C-NMR (125 MHz, acetone-d_6): δ 56.8 (CH_3), 115.6 (2CH), 117.2 (CH), 117.4 (CH), 126.5 (CH), 127.9 (CH), 128.1 (CH), 129.3 (C_{quat}), 130.7 (C_{quat}), 131.30 (2CH), 131.32 (CH), 131.5 (CH), 131.6 (CH), 134.4 (CH), 133.4 (C_{quat}), 136.6 (C_{quat}), 149.3 (C_{quat}), 152.2 (C_{quat}), 164.0 (C_{quat}), 166.4 (C_{quat}). MALDI–TOF (DIT, $CHCl_3$, *m/z*): 362 ($[M + H]^+$), 330 ($[M - S]^+$). IR (KBr): $\tilde{\nu}$ = 2839 cm^1 (w), 1601 (s), 1561 (m), 1501 (s), 1458 (m), 1321 (m), 1259 (s), 1169 (s), 1159 (s), 1029 (s), 823 (s), 747 (m), 622 (w), 561 (w), 514 (w). Anal. calcd. for $C_{22}H_{16}FNOS$ (361.4): C 73.11, H 4.46, N 3.88; Found: C 72.83, H 4.64, N 3.70.

*4-(4-Chlorophenyl)-2-ferrocenylbenzo[b][1,5] thiazepine (***4j***)*

Following the general procedure **4j** was obtained as red crystals, mp 80 °C (for details see Table 4). Red crystals, mp 80 °C. ^{1}H-NMR (500 MHz, acetone-d_6): δ 4.14 (s, 5H), 4.47 (t, ^3J = 1.8 Hz, 2H), 4.95 (t, ^3J = 1.8 Hz, 2H), 6.90 (s, 1H), 7.25 (dt, ^3J = 7.7 Hz, ^4J = 1.2 Hz, 1H), 7.36 (dd, ^3J = 7.7 Hz, ^4J = 1.2 Hz, 1H), 7.44 (dt, ^3J = 7.7 Hz, ^4J = 1.2 Hz, 1H), 7.53–7.56 (m, 3H), 8.07 (d, ^3J = 8.4 Hz, 2H). ^{13}C-NMR (125 MHz, acetone-d_6): δ 70.1 (2CH), 71.7 (5CH), 72.6 (2CH), 84.9 (C_{quat}), 121.1 (CH), 128.0 (CH), 128.3 (CH), 130.4 (2CH), 131.2 (C_{quat}), 131.25 (2CH), 131.28 (CH), 134.7 (CH), 138.3 (C_{quat}), 140.2 (C_{quat}), 152.2 (C_{quat}), 153.2 (C_{quat}), 166.1 (C_{quat}). MALDI–TOF (DIT, $CHCl_3$, *m/z*): 456 ($[M + H]^+$). IR (KBr): $\tilde{\nu}$ = 1638 cm^{-1} (m), 1604 (m), 1590 (s), 1560 (s), 1485 (m), 1458 (m), 1399 (m), 1304 (m), 1216 (m), 1171 (m), 1105 (m), 1090 (s), 1052 (m), 1029 (m), 1011 (s), 963 (w), 891 (w), 820 (s), 783 (m), 756 (s), 729 (m), 671 (w), 589 (w), 545 (w), 524 (w). Anal. calcd. for $C_{25}H_{18}ClFeNS$ (455.8): C 65.88, H 3.98, N 3.07; Found: C 65.79, H 4.24, N 2.94.

*4-(4-(4-Methoxyphenyl)benzo[b][1,5]thiazepin-2-yl) benzonitrile (***4k***)*

Following the general procedure **4k** was obtained as a yellow solid, mp 126 °C (for details see Table 4). ^{1}H-NMR (500 MHz, acetone-d_6): δ 3.88 (s, 3H), 7.05 (d, ^3J = 8.9 Hz, 2H), 7.23–7.26 (m, 1H), 7.27 (s, 1H), 7.36–7.38 (m, 1H), 7.42–7.46 (m, 1H), 7.53–7.55 (m, 1H), 7.84 (d, ^3J = 8.7 Hz, 2H), 8.09 (d, ^3J = 8.9 Hz, 2H), 8.15 (d, ^3J = 8.7 Hz, 2H). ^{13}C-NMR (125 MHz, acetone-d_6): δ 56.8 (CH_3), 114.5 (C_{quat}), 115.7 (2CH), 120.0 (C_{quat}), 128.1 (CH), 128.3 (CH), 128.9 (C_{quat}), 129.4 (CH), 130.1 (2CH), 131.4 (2CH), 131.5 (CH), 131.1 (C_{quat}), 134.3 (2 CH), 134.4 (CH), 144.5 (C_{quat}), 148.3 (C_{quat}), 152.0 (C_{quat}), 164.1 (C_{quat}), 166.0 (C_{quat}). MALDI–TOF (DIT, $CHCl_3$, *m/z*): 369 ($[M + H]^+$), 337 ($[M-S]^+$). IR (KBr): $\tilde{\nu}$ = 2935 cm^{-1} (w), 2838 (w), 2222 (s), 1601 (s), 1561 (s), 1509 (m), 1498 (m), 1456 (w), 1419 (m), 1316 (s), 1249 (s), 1209 (w), 1190 (w), 1170 (s), 1111 (m), 1068 (w), 1029 (m), 938 (w), 864 (w), 847 (w), 834 (s), 817 (m), 784 (w), 759 (w), 746 (m), 685 (w), 637 (w), 624 (w), 540 (m), 523 (w), 509 (w). Anal. calcd. for $C_{23}H_{16}N_2OS$ (368.5): C 74.98, H 4.38, N 7.60; Found: C 74.83, H 4.31, N 7.49.

*4-(4-Methoxyphenyl)-2-(trimethylsilyl)benzo[b][1,5]thiazepine (***4l***)*

Following the general procedure **4l** was obtained as a yellow solid, mp 106 °C (for details see Table 4). ^{1}H-NMR (500 MHz, acetone-d_6): δ 0.26 (s, 9H), 3.87 (s, 3H), 6.93 (s, 1H), 7.03 (d, ^3J = 8.9 Hz, 2H), 7.15–7.18 (m, 1H), 7.27–7.32 (m, 2H), 7.35–7.39 (m, 1H), 7.96 (d, ^3J = 8.9 Hz, 2H). ^{13}C-NMR (125 MHz, acetone-d_6): δ –1.6 ($3CH_3$), 56.3 (CH_3), 115.2 (2CH), 127.47 (CH), 127.54 (CH), 130.5 (CH), 130.6 (2CH), 130.9 (C_{quat}), 132.8 (C_{quat}), 133.4 (CH), 138.3 (C_{quat}), 152.1 (C_{quat}), 159.2 (C_{quat}), 163.5 (C_{quat}), 166.9 (C_{quat}). MALDI–TOF (DIT, $CHCl_3$, *m/z*): 340 ($[M + H]^+$). IR (KBr): $\tilde{\nu}$ = 3051 cm^{-1} (w), 2999 (w), 2956 (m), 2835 (w), 1638 (m), 1596 (s), 1562 (m), 1510 (m), 1456 (m), 1419 (m), 1314 (m), 1292 (w), 1257 (s), 1177 (s), 1117 (w), 1067 (w), 1020 (m), 956 (w), 839 (s), 806 (m), 778 (w), 759 (s), 698 (w), 625 (w), 605 (w), 544 (w), 530 (w). Anal. calcd. for $C_{19}H_{21}NOSSi$ (339.5): C 67.21, H 6.23, N 4.13; Found: C 67.24, H 6.34, N 3.77.

*7-Chloro-2-phenyl-4-(thien-2-yl)benzo[b][1,4] thiazepine (***4m***)*

Following the general procedure **4m** was obtained as a yellow solid, mp 146 °C (for details see Table 4). ^{1}H-NMR (500 MHz, acetone-d_6): δ 7.21–7.22 (m, 1H), 7.28–7.31 (m, 3H), 7.45–7.48 (m, 3H), 7.55 (d, ^3J = 8.3 Hz, 1H), 7.78–7.79

(m, 1H), 7.81–7.83 (m, 1H), 7.97–7.99 (m, 2H). ^{13}C-NMR (125 MHz, acetone-d_6): δ 124.7 (CH), 126.6 (CH), 127.4 (CH), 128.7 ($2CH_2$), 129.1 (CH), 129.7 (2 CH), 131.0 (CH), 131.3 (CH), 132.5 (CH), 133.3 (C_{quat}), 134.9 (CH), 135.8 (C_{quat}), 138.9 (C_{quat}), 146.5 (C_{quat}), 150.9 (C_{quat}), 152.1 (C_{quat}), 162.3 (C_{quat}). MALDI–TOF (DIT, $CHCl_3$, *m/z*): 354 ($[M + H]^+$), 322 ($[M - S]^+$). IR (KBr): $\tilde{\nu}$ = 1601 cm^1 (m), 1562 (s), 1544 (m), 1489 (w), 1452 (m), 1422 (s), 1378 (w), 1351 (w), 1318 (w), 1240 (w), 1213 (w), 1198 (w), 1130 (w), 1091 (m), 1054 (m), 1006 (w), 935 (w), 916 (w), 885 (m), 873 (m), 857 (w), 846 (m), 873 (m), 833 (m), 801 (s), 758 (s), 716 (s), 691 (s), 667 (w), 652 (w), 564 (w), 533 (w). Anal. calcd. for $C_{19}H_{12}ClNS_2$ (353.9): C 65.48, H 3.42, N 3.96; Found: C 65.82, H 3.23, N 3.73.

*7-Chloro-4-(4-chlorophenyl)-2-phenylbenzo[b][1,5] thiazepine (***4n***)*

Following the general procedure **4n** was obtained as a yellow solid, mp 111 °C (for details see Table 4). ^{1}H-NMR (500 MHz, acetone-d_6): δ 7.20 (s, 1H), 7.43–7.48 (m, 2H), 7.55–7.64 (m, 4H), 7.91 (m, ^3J = 8.9 Hz, 1H), 8.05 (s, 1H), 8.15 (d, ^3J = 8.7 Hz, 2H), 8.40 (d, ^3J = 8.9 Hz, 2H). ^{13}C-NMR (125 MHz, acetone-d_6): δ 120.8 (CH), 126.4 (CH), 129.5 (2CH), 130.4 (CH), 130.6 (2CH), 130.7 (CH), 131.0 (2CH), 131.5 (2CH), 131.6 (CH), 134.2 (CH), 135.8 (C_{quat}), 141.0 (C_{quat}), 151.4 (C_{quat}), 151.9 (C_{quat}), 153.1 (C_{quat}), 158.0 (C_{quat}), 165.7 (C_{quat}). MALDI–TOF (DIT, $CHCl_3$, *m/z*): 382 ($[M + H]^+$), 350 ($[M - S]^+$). IR (KBr): $\tilde{\nu}$ = 1655 cm^1 (w), 1589 (s), 1560 (m), 1543 (m), 1485 (s), 1448 (m), 1417 (m), 1400 (m), 1354 (m), 1320 (m), 1200 (m), 1172 (m), 1093 (s), 1078 (s), 1012 (m), 968 (w), 909 (w), 876 (m), 836 (s), 806 (s), 758 (s), 701 (m), 685 (m), 652 (w), 616 (w), 563 (w), 525 (w). Anal. calcd. for $C_{21}H_{13}Cl_2NS$ (382.3): C 65.97, H 3.43, N 3.66; Found: C 65.96, H 3.59, N 3.61.

Acknowledgments The support of this work by the Fonds der Chemischen Industrie and the CEM GmbH is gratefully acknowledged. The authors also cordially thank Cand.-Chem. Patrick Bongen for experimental assistance, and the BASF AG for the generous donation of chemicals.

References

1. Bariwal JB, Upadhyay KD, Manvar AT, Trivedi JC, Singh JS, Jain KS, Shah AK (2008) 1,5-Benzothiazepine, a versatile pharmacophore: a review. Eur J Med Chem 43:2279–2290. doi:10.1016/j.ejmech.2008.05.035
2. Mane RA, Ingle DB (1982) Synthesis and biological activity of some new 1,5-benzothiazepines containing thiazole moiety: 2-aryl-4-(4-methyl-2-substituted-aminothiazol-5-yl)-2,3-dihydro-1,5-benzothiazepines. Indian J Chem Sect B 21:973–974
3. Jadhav KP, Ingle DB (1982) Synthesis of 2,4-diaryl-2,3-dihydro-1,5-benzothiazepines and their 1,1-dioxides as antibacterial agents. Indian J Chem Sect B 22:180–182
4. Attia A, Abdel-Salam OI, Abo-Ghalia MH, Amr AE (1995) Chemical and biological reactivity of newly synthesized 2-chloro-6-ethoxy-4-acetylpyridine. Egypt J Chem 38:543–554
5. Reddy RJ, Ashok D, Sarma PN (1993) Synthesis of 4,6-bis(2'-substituted-2′,3′-dihydro-1,5-benzothiazepin-4′-yl)resorcinols as potential antifeedants. Indian J Chem Sect B 32:404–406
6. Satyanarayana K, Rao MNA (1993) Synthesis of 3-[4-[2,3-dihydro-2-(substituted aryl)-1,5-benzothiazepin-4-yl]phenyl]sydnones as potential antiinflammatory agents. Indian J Pharm Sci 55: 230–233
7. De Sarro G, Chimirri A, De Sarro A, Gitto R, Grasso S, Zappala M (1995) 5*H*-[1,2,4]Oxadiazolo[5,4-*d*][1,5]benzothiazepines as anticonvulsant agents in DBA/2 mice. Eur J Med Chem 30:925–929. doi:10.1016/0223-5234(96)88311-5
8. Swellem RH, Allam YA, Nawwar GAM (1999) Cinnamoylacetonitrile in heterocyclic synthesis, Part 7. Simple synthesis of benzothiazepines, pyrones and oxazolopyridine. Z Naturforsch B 54:1197–1201
9. Dubey PK, Naidu A, Kumar CR, Reddy PVVP (2003) Preparation of 4-(1-alkylbenz[d]imidazol-2-yl)-2-phenyl-2,3-dihydrobenzo[b][1,4]thiazepines. Indian J Chem Sect B 42:1701–1705
10. Lévai A (1986) Synthesis of benzothiazepines (review). Chem Heterocycl Comp 22:1161–1170. doi:10.1007/BF00471794
11. Lévai A (2000) Synthesis and chemical transformation of 1,5-benzothiazepines. J Heterocycl Chem 37:199–214
12. Ried W, Marx W (1957) Über heterocyclische Siebenringsysteme, VIII. Synthesen Kondensierter Gliedriger Heterocyclen mit 1 Stickstoff- und 1 Schwefelatom. Chem Ber 90: 2683–2687. doi:10.1002/cber.19570901139
13. Stephens WD, Field L (1959) A seven-membered heterocycle from O-aminobenzenethiol and chalcone. J Org Chem 24:1576. doi:10.1021/jo01092a610
14. Lévai A, Bognar R (1976) Oxazepines and thiazepines, II. Synthesis of 3-dihydro-2,4-diphenyl-1,5-benzothiazepines by the reaction of 2-aminothiophenol with chalcones substituted in ring B. Acta Chim Acad Sci Hung 88:293–300
15. Lévai A, Bognar R (1977) Oxazepines and thiazepines, III. Synthesis of 3-dihydro-2,4-diphenyl-1,5-benzothiazepines by the reaction of 2-aminothiophenol with chalcones substituted in ring A. Acta Chim Acad Sci Hung 92:415–419
16. Lévai A, Bognar R, Kajtar J (1980) Oxazepines and thiazepines. VII. Synthesis and circular dichroism of 2, 3-dihydro-2,4-diphenyl-1,5-benzothiazepine glycosides. Acta Chim Acad Sci Hung 103:27–32
17. Duddeck H, Kaiser M, Lévai A (1985) Oxazepine und Thiazepine, XVI. 1H- und ^{13}C-NMR-Untersuchungen zur Struktur von Benzothiazepinon-Derivaten. Liebigs Ann Chem 869–876. doi:10.1002/jlac.198519850424
18. Aryaa K, Dandia A (2008) The expedient synthesis of 1,5-benzothiazepines as a family of cytotoxic drugs. Bioorg Med Chem Lett 18:114–119. doi:10.1016/j.bmcl.2007.11.002
19. Ried W, König E (1972) Reaktionen von Acetylenketonen mit nucleophilen Agenzien vom Typ des *o*-Phenylendiamins, *o*-Aminothiophenols und *N*1-disubstituierten Hydrazins. Liebigs Ann Chem 755:24–31. doi:10.1002/jlac.19727550105
20. Nakhamanovich AS, Glotova TE, Skvortsova GG, Komarova TN, Skorobogatova VI, Mansurov YA (1982) Bull Acad Sci USSR Chem Ser 31:1221–1224
21. Blitzke T, Sicker D, Wilde H (1995) Diethyl 2-oxopent-3-ynedioate: synthesis and first cyclizations of a novel, reactive alkyne. Synthesis 236–238. doi:10.1055/s-1995-3898
22. Cabarrocas G, Rafel S, Ventura M, Villalgordo JM (2000) A new approach toward the stereoselective synthesis of novel quinolyl

glycines: synthesis of the enantiomerically pure quinolyl- β-amino alcohol precursors. Synlett 595–598. doi:10.1055/s-2000-6625
23. Cabarrocas G, Ventura M, Maestro M, Mahia J, Villalgordo JM (2001) Synthesis of novel optically pure quinolyl-β-amino alcohol derivatives from 2-amino thiophenol and chiral α-acetylenic ketones and their IBX-mediated oxidative cleavage to *N*-Boc quinolyl carboxamides. Tetrahedron-Asymmetr 12:1851–1863. doi:10.1016/S0957-4166(01)00308-1
24. Nagarapu L, Ravirala N, Akkewar D (2001) Benzothiazepine fused heterocycles IV: a convenient synthesis of benzo[b][1,5]thiazepines using MCM-41(H) zeolite. Heterocycl Commun 7: 237–242
25. Müller TJJ, D'Souza DM (2008) Diversity oriented syntheses of functional π-systems by multi-component and domino reactions. Pure Appl Chem 80:609–620. doi:10.1351/pac200880030609
26. Müller TJJ (2007) Diversity-oriented synthesis of chromophores by combinatorial strategies and multi-component reactions. In: Müller TJJ, Bunz UHF (eds) Functional organic materials. Syntheses, strategies, and applications. Wiley-Vch, Weinberg, p 179
27. Schreiber SL, Burke MD (2004) A planning strategy for diversity-oriented synthesis. Angew Chem Int Ed 43:46–58. doi:10.1002/anie.200300626
28. Burke MD, Berger EM, Schreiber SL (2003) Generating diverse skeletons of small molecules combinatorially. Science 302: 613–618. doi:10.1126/science.1089946
29. Arya P, Chou DTH, Baek MG (2001) Diversity-based organic synthesis in the era of genomics and proteomics. Angew Chem Int Ed 40:339–346. doi:10.1002/1521-3773(20010119)40:2<339::AID-ANIE339>3.0.CO;2-J
30. Cox B, Denyer JC, Binnie A, Donnelly MC, Evans B, Green DVS, Lewis JA, Mander TH, Merritt AT, Valler MJ, Watson SP (2000) Application of high-throughput screening techniques to drug discovery. Prog Med Chem 37:83–133
31. Schreiber SL (2000) Target-oriented and diversity-oriented organic synthesis in drug discovery. Science 287:1964–1969. doi:10.1126/science.287.5460.1964
32. Zhu J, Bienayme H (eds) (2005) Multicomponent reactions. Wiley-VCH, Weinheim
33. D'Souza DM, Müller TJJ (2007) Multi-component syntheses of heterocycles by transition metal catalysis. Chem Soc Rev 36: 1095–1108. doi:10.1039/b608235c
34. Dömling A (2006) Recent developments in isocyanide based multicomponent reactions in applied chemistry. Chem Rev 106:17–89. doi:10.1021/cr0505728
35. Orru RVA, de Greef M (2003) Recent advances in solution-phase multicomponent methodology for the synthesis of heterocyclic compounds. Synthesis 1471–1499. doi:10.1055/s-2003-40507
36. Bienaymé H, Hulme C, Oddon G, Schmitt P (2000) Maximizing synthetic efficiency: multi-component transformations lead the way. Chem Eur J 6: 3321–3329. doi:10.1002/1521-3765(20000915)6:18<3321::AID-CHEM3321>3.0.CO;2-A
37. Dömling A, Ugi I (2000) Multicomponent reactions with isocyanides. Angew Chem Int Ed 39:3168–3210. doi:10.1002/1521-3773(20000915)39:18<3168::AID-ANIE3168>3.0.CO;2-U
38. Ugi I, Dömling A, Werner B (2000) Since 1995 the new chemistry of multicomponent reactions and their libraries, including their heterocyclic chemistry. J Heterocycl Chem 37:647–658
39. Weber L, Illgen K, Almstetter M (1999) Discovery of new multi component reactions with combinatorial methods. Synlett 366–374. doi:10.1055/s-1999-2612
40. Armstrong RW, Combs AP, Tempest PA, Brown SD, Keating TA (1996) Multiple-component condensation strategies for combinatorial library synthesis. Acc Chem Res 29:123–131. doi:10.1021/ar9502083
41. Ugi I, Dömling A, Hörl W (1994) Multicomponent reactions in organic chemistry. Endeavour 18:115–122. doi:10.1016/S0160-9327(05)80086-9
42. Posner GH (1986) Multicomponent one-pot annulations forming 3 to 6 bonds. Chem Rev 86:831–844. doi:10.1021/cr00075a007
43. Willy B, Müller TJJ (2008) Consecutive multi-component syntheses of heterocycles via palladium-copper catalyzed generation of alkynones. ARKIVOC Part I:195–208
44. Müller TJJ (2007) Multi-component Syntheses of heterocycles initiated by palladium catalyzed generation of alkynones and chalcones. Chim Oggi/Chem Today 25:70–78
45. Müller TJJ (2006) Multi-component syntheses of heterocycles by virtue of palladium catalyzed generation of alkynones and chalcones. Target Heterocycl Syst 10:54–65
46. Willy B, Müller TJJ (2009) Multi-component heterocycle syntheses via catalytic generation of alkynones. Curr Org Chem 13: 1777–1790
47. Takahashi S, Kuroyama Y, Sonogashira K, Hagihara N (1980) A convenient synthesis of ethynylarenes and diethynylarenes. Synthesis 627–630. doi:10.1055/s-1980-29145
48. Sonogashira K (1998) In: Diederich F, Stang PJ (eds) Metal catalyzed cross-coupling reactions. Wiley-VCH, Weinheim pp 203–229
49. Sonogashira K (2002) Development of Pd–Cu catalyzed cross-coupling of terminal acetylenes with sp2-carbon halides. J Organomet Chem 653: 46–49. doi:10.1016/S0022-328X(02)01158-0
50. Negishi EI, Anastasia L (2003) Palladium-catalyzed alkynylation. Chem Rev 103:1979–2018. doi:10.1021/cr020377i
51. Marsden JA, Haley MM (2004). In: de Meijere A, Diederich F (eds) Metal catalyzed cross-couping reactions. Wiley-VCH, Weinheim, pp 319–345
52. Doucet H, Hierso JC (2007) Palladium-based catalytic systems for the synthesis of conjugated enynes by Sonogashira reactions and related alkynylations. Angew Chem Int Ed 46:834–871. doi:10.1002/anie.200602761
53. Yin L, Liebscher J (2007) Carbon–carbon coupling reactions catalyzed by heterogeneous palladium catalysts. Chem Rev 107: 133–173. doi:10.1021/cr0505674
54. Toda Y, Sonogashira K, Hagihara N (1977) A convenient synthesis of 1-alkynyl ketones and 2-alkynamides. Synthesis 777–778. doi:10.1055/s-1977-24574
55. D'Souza DM, Müller TJJ (2008) Catalytic alkynone generation by sonogashira reaction and its application in three-component pyrimidine synthesis. Nat Protoc 3:1660–1665. doi:10.1038/nprot.2008.152
56. Karpov AS, Müller TJJ (2003) A new entry to a three component pyrimidine synthesis by tms-ynones via Sonogashira-coupling. Org Lett 5:3451–3454. doi:10.1021/ol035212q10.1021/ol035212q
57. Willy B, Müller TJJ (2008) Regioselective three-component synthesis of highly fluorescent 1,3,5-trisubstituted pyrazoles. Eur J Org Chem 4157–4168. doi:10.1002/ejoc.200800444
58. Karpov AS, Müller TJJ (2003) Straightforward Novel one-pot enaminone and pyrimidine syntheses by coupling–addition–cyclocondensation sequences. Synthesis 2815–2826. doi:10.1055/s-2003-42480
59. Karpov AS, Merkul E, Rominger F, Müller TJJ (2005) Concise syntheses of meridianins via carbonylative alkynylation and a novel four-component pyrimidine synthesis. Angew Chem Int Ed 44:6951–6956. doi:10.1002/anie.200501703
60. Merkul E, Oeser T, Müller TJJ (2009) Consecutive three-component synthesis of ynones by decarbonylative Sonogashira coupling. Chem Eur J 15:5006–5011. doi:10.1002/chem.200900119
61. Willy B, Dallos T, Rominger F, Schönhaber J, Müller TJJ (2008) Three-component synthesis of cryo-fluorescent 2,4-disub-

stituted 3-*H*benzo[b][1,4]diazepines—conformational controlof emission properties. Eur J Org Chem 4796–4805. doi:10.1002/ejoc.200800619
62. Applying the semiempirical AM1 model as implemented in PC Spartan Pro (1999) Wavefunction Inc, Irvine, CA, USA
63. Thompson MA, Zerner MC (1991) A theoretical examination of the electronic structure and spectroscopy of the photosynthetic reaction center from Rhodopseudomonas viridis. J Am Chem Soc 113: 8210–8215. doi:10.1021/ja00022a003
64. Thompson MA, Glendening ED, Feller D (1994) The nature of K^+/crown ether interactions: a hybrid quantum mechanical-molecular mechanical study. J Phys Chem 98:10465–10476. doi:10.1021/j100092a015
65. Thompson MA, Schenter GK (1995) Excited states of the bacteriochlorophyll b dimer of rhodopseudomonas viridis: a QM/MM study of the photosynthetic reaction center that includes MM polarization. J Phys Chem 99: 6374–6386. doi:10.1021/j100017a017
66. Thompson MA (1996) QM/MMpol: a consistent model for solute/solvent polarization. Application to the aqueous solvation and spectroscopy of formaldehyde, acetaldehyde, and acetone. J Phys Chem 100:14492–14507. doi:10.1021/jp960690m
67. Zerner MC, Loew GH, Kirchner RF, Mueller-Westerhoff UT (1980) An intermediate neglect of differential overlap technique for spectroscopy of transition-metal complexes. Ferrocene. J Am Chem Soc 102:589–599. doi:10.1021/ja00522a025
68. As implemented in ArgusLab 4.0 (2004) Thompson MA, Planaria Software LLC, Seattle, WA, USA