SCIENCE CHINA
Chemistry

• ARTICLES •

October 2012 Vol.55 No.10: 2154–2160
doi: 10.1007/s11426-012-4665-z

Amberlyst-15® in PEG: A novel catalytic system for the facile and efficient one-pot synthesis of benzothiazolo-[2,3-*b*]-quinazolinone derivatives

MAZAAHIR Kidwai*‡, RITIKA Chauhan & DIVYA Bhatnagar

Green Chemistry Research Laboratory, Department of Chemistry, University of Delhi, Delhi-110007, India

Received November 23, 2011; accepted December 22, 2011; published online July 5, 2012

A simple and convenient approach for the synthesis of tetraheterocyclic benzothiazolo-[2,3-*b*]-quinazolin-1-ones has been developed utilizing the MCR methodology, which involves the condensation of 2-aminobenzothiazole, cyclic β-diketones and various aldehydes using Amberlyst-15® in PEG 400 as an environmentally benign and reusable catalyst system. Environmental benignity, recyclability, cost-effectiveness, easy workup and excellent yields are the major attributes of this one-pot procedure.

Amberlyst-15®, benzothiazolo-[2,3-*b*]-quinazolinones, multi-component reaction, reusability, PEG (polyethylene glycol), green chemistry

1 Introduction

Multi-component reactions (MCRs), an important subclass of tandem reactions, are one-pot processes in which three or more accessible components react to form a single product that incorporates essentially most or all atoms of the reactants used [1]. One-pot multi-component strategies grant remarkable advantages over conventional bimolecular reactions owing to their convergence, atom-economy, operational simplicity, structural diversity and shortness of the synthetic pathway [2]. MCRs have recently gained a new dimension in the field of designing methods to produce elaborate libraries of biologically active compounds [3].

The fusion of biodynamic heterosystems has emerged as a useful tool for the design of new molecular frameworks for potential drugs with diverse pharmacological activities [4]. Quinazolines are very interesting heterocycles [5] as they serve as building blocks in numerous natural and synthetic products that exhibit a wide spectrum of biological and pharmacological activities. Thiazoloquinazolines have also been an important class of heterocycles in drug research, as they incorporate both biodynamic heterosystems thiazole and quinazoline which have shown significant anticancer activities [6]. Additionally, thiazoloquinazolines have also been identified as cyclin-dependent kinase (CDK) and glycogen synthase kinase-3 (GSK-3) inhibitors [7]. In view of the importance of these polyheterocyclic compounds, several methods have been quoted in the literature [8–14]. However, these methods suffer from drawbacks such as prolonged reaction time, use of volatile organic solvents, harmful catalysts, low yields and harsh reaction conditions. Therefore, the search of improved catalysts for the synthesis of benzothiazoloquinazolinone derivatives using an eco-friendly approach is of prime importance.

Development of efficient and practical catalysts for organic synthesis is of considerable interest to both academia and industry [15]. In recent years, a tremendous upsurge of interest has been observed in carrying out various chemical transformations under heterogeneous conditions owing to simplicity in operation, remarkable recyclability and

*Corresponding author (email: kidwai.chemistry@gmail.com)
‡Presently working as Vice-Chancellor, Jiwaji University, Gwalior (M. P.), India (On Deputation from Department of Chemistry, University of Delhi, Delhi-110007, India)

eco-friendly nature [16]. In this regard, Amberlyst-15® possesses unique features such as environmental compatibility, non-toxicity, reusability, non-corrosivity, chemical and physical stability and can be used over a prolonged duration of time [17]. Owing to the numerous advantages associated with this cheap and non-hazardous catalyst, Amberlyst-15® has been explored as a powerful catalyst for a plethora of organic reactions [18–21]. Recently, polyethylene glycol (PEG) and its monomethyl ethers have emerged as alternative green reaction media with unique properties including thermal stability, commercial availability, non-volatility, immiscibility with a number of organic solvents, and recyclability. On the other hand, PEGs are inexpensive, completely non-halogenated, easily degradable and possess low toxicity [22]. The use of PEGs as reaction solvent has received great amount of attention in synthetic organic chemistry.

As a part of our continuing efforts in laboratory towards the development of cheap and environmentally benign methodologies for organic reactions [23], we decided to couple the heterogeneous catalyst Amberlyst-15® with the recyclable solvent PEG 400 for the mild and highly efficient three-component synthesis of benzothiazolo-[2,3-*b*]-quinazolin-1-one derivatives.

2 Experimental

2.1 Materials and methods

All chemicals were purchased from Sigma-Aldrich and were used without further purification. All reactions and the purity of benzothiazolo-[2,3-*b*]-quinazolin-1-ones were monitored by thin-layer chromatography (TLC) using aluminum plates coated with silica gel F_{254} plates (Merck) using 30% ethyl acetate and 70% petroleum ether (*v*/*v*) as an eluent. The spots were detected either under UV light or by placing in an iodine chamber. Melting points were determined in open capilliaries using a Thomas Hoover melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FTIR-1710 spectrophotometer using KBr pellets per nujol film. ^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL JNM-ECX 400P FT NMR system using tetramethylsilane (TMS) as an internal standard and the value of chemical shift is in the δ scale and *J* value is in hertz (Hz). Elemental analysis was performed on a Hereaus CHN rapid analyzer. The temperature of the reaction mixture was measured through a non-contact infrared mini gun thermometer (AZ minigun type, model 8868).

2.2 General procedure for the synthesis of benzothiazolo-[2,3-*b*]-quinazolin-1-one derivatives

A 50 mL round-bottom flask was filled with 2-amino-benzothiazole **1** (1 mmol), aldehyde **2(a–p)** (1 mmol), cyclic β-diketone **3(a–b)** (1 mmol) and Amberlyst-15® (100 mg) followed by PEG 400 (2 mL) as a solvent. The reaction mixture was then stirred at 50 °C until the reaction was complete. The progress of the reaction was monitored using TLC plates. Upon completion of the reaction, the reaction mixture was cooled in a dry ice-acetone bath to precipitate the PEG 400 and was extracted with ether (5 mL × 3) (PEG 400 being insoluble in ether). The ether layer was decanted, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to produce the crude product. The recovered PEG 400 phase along with the catalyst was reused for consecutive runs. The crude product, thus obtained was subjected to purification by column chromatography on silica gel (100–200 mesh size) using hexane/ethyl acetate in varying proportions as eluent which afforded the respective benzothiazoloquinazolinones, **4(a–q)**. The structures of all the products were unambiguously established on the basis of spectral analysis (IR, ^{1}H NMR, ^{13}C NMR), elemental analysis and melting point determination [24, 25]. Spectral data for the synthesized derivatives are described below.

2.3 Regeneration of the catalyst system

After the reaction was complete, the reaction mixture was cooled in dry-ice acetone bath to precipitate the PEG 400 and was extracted with ether. The ether layer was decanted, dried over anhydrous Na_2SO_4 and concentrated under vaccuo to produce the crude product. The PEG 400 phase along with resin (Amberlyst-15®) was used as such for subsequent runs (four runs) with fresh substrates under the same conditions. The recovered catalyst system showed almost the same catalytic efficiency as the fresh catalyst.

2.4 Spectral data of the synthesized compounds

12-Phenyl-2,3,4,12-tetrahydro-benzo[4,5]thiazolo[2,3-b] quinazolin-1-one ***(4a)***

IR ν_{max} (cm^{-1}, nujol): 3317, 2950, 1721, 1589, 1537, 1379, 754; ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ: 1.99–2.05 (m, 2H), 2.38–2.47 (m, 2H), 2.56–2.66 (m, 2H), 5.47 (s, 1H, ArCH), 7.09–7.20 (m, 5H, Ar–H), 7.28–7.59 (m, 4H, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 20.0, 29.8, 42.8, 56.2, 112.7, 116.4, 119.1, 120.9, 122.3, 125.8, 126.0, 126.4, 128.1, 130.5, 137.8, 152.4, 165.8, 192.1; Anal calcd. for $C_{20}H_{16}N_2OS$: C, 72.26; H, 4.85; N, 8.43; Found: C, 72.08; H, 4.68; N, 8.27.

12-(4-Chloro-phenyl)-2,3,4,12-tetrahydro-benzo[4,5]thiazolo [2,3-b]quinazolin-1-one ***(4b)***

IR ν_{max} (cm^{-1}, nujol): 3318, 2950, 1719, 1588, 1534, 1376, 544; ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ: 1.98–2.05 (m, 2H), 2.34–2.48 (m, 2H), 2.54–2.65 (m, 2H), 5.40 (s, 1H, ArCH), 7.01–7.22 (m, 4H, Ar–H), 7.29–7.83 (m, 4H, Ar–H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 20.0, 33.4, 41.6, 112.4, 116.1, 120.9, 126.0, 127.9, 128.2, 129.4, 130.2, 130.9, 136.5, 140.8, 145.6, 165.8, 192.3; Anal calcd. for

$C_{20}H_{15}ClN_2OS$: C, 65.48; H, 4.12; N, 7.64; Found: C, 65.28; H, 3.96; N, 7.48.

12-(4-Methoxy-phenyl)-2,3,4,12-tetrahydro-benzo[4,5]thiazolo [2,3-b]quinazolin-1-one ***(4c)***

IR ν_{max} (cm^{-1}, nujol): 3308, 2952, 1722, 1588, 1537, 1377, 1243, 752; ^1H NMR ($CDCl_3$, TMS, 400 MHz) δ: 1.99–2.05 (m, 2H), 2.33–2.48 (m, 2H), 2.55–2.65 (m, 2H), 3.77 (s, 3H, OCH_3), 5.41 (s, 1H, ArCH), 6.79–7.01 (m, 4H, Ar–H), 7.13–7.60 (m, 4H, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 20.1, 33.5, 41.2, 55.2, 112.2, 113.5, 116.7, 119.4, 126, 127.5, 129.8, 130.2, 136.7, 145.2, 151.9, 157.5, 165.7, 192.1; Anal calcd. for $C_{21}H_{18}N_2O_2S$: C, 69.59; H, 5.01; N, 7.73; Found: C, 69.45; H, 4.91; N, 7.56.

12-(4-Hydroxy-phenyl)-2,3,4,12-tetrahydro-benzo[4,5]thiazolo [2,3-b]quinazolin-1-one ***(4d)***

IR ν_{max} (cm^{-1}, nujol): 3448, 2987, 2251, 1647, 1376, 1249, 1053, 760; ^1H NMR (DMSO-d_6, TMS, 400 MHz) δ: 1.98–2.04 (m, 2H), 2.12–2.19 (m, 2H), 2.22–2.30 (m, 2H), 5.34 (s, 1H, ArCH), 6.55–6.69 (m, 4H, Ar-H), 6.85–7.06 (m, 4H, Ar–H), 8.86 (br s, 1H, OH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 20.0, 33.5, 40.8, 54.6, 112.2, 115.4, 116.1, 117.2, 126.0, 128.4, 129.6, 131.3, 135.5, 143.8, 152.7, 157.4, 164.2, 192.3; Anal calcd. for $C_{20}H_{16}N_2O_2S$: C, 68.94; H, 4.63; N, 8.04; Found: C, 68.78; H, 4.48; N, 7.86.

12-(4-Nitro-phenyl)-2,3,4,12-tetrahydro-benzo[4,5]thiazolo [2,3-b]quinazolin-1-one ***(4e)***

IR ν_{max} (cm^{-1}, nujol): 3321, 3193, 2951, 2252, 1722, 1604, 1346, 754; ^1H NMR ($CDCl_3$, TMS, 400 MHz) δ: 1.98–2.07 (m, 2H), 2.36–2.52 (m, 2H), 2.57–2.69 (m, 2H), 5.47 (s, 1H, ArCH), 7.11–7.60 (m, 4H, Ar–H), 7.87–8.41 (m, 4H, Ar–H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 20.0, 33.4, 41.6, 49.6, 112.3, 115.7, 116.4, 119.3, 123.4, 126.0, 127.4, 130.0, 130.9, 144.1, 146.0, 148.7, 151.7, 162.8, 192.6; Anal calcd. for $C_{20}H_{15}N_3O_3S$: C, 63.65; H, 4.01; N, 11.13; Found: C, 63.47; H, 3.88; N, 10.97.

12-Benzo[1,3]dioxol-5-yl-2,3,4,12-tetrahydro-benzo[4,5] thiazolo[2,3-b]quinazolin-1-one ***(4f)***

IR ν_{max} (cm^{-1}, KBr): 3301, 2964, 1720, 1603, 1484, 1375, 1241, 777; ^1H NMR ($CDCl_3$, TMS, 400 MHz) δ: 2.01–2.06 (m, 2H), 2.46–2.50 (m, 2H), 2.54–2.60 (m, 2H), 5.37 (s, 1H, ArCH), 5.92 (s, 2H, CH_2), 6.54–6.71 (m, 4H, Ar–H), 6.78–7.57 (m, 3H, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 20.0, 33.5, 42.6, 51.7, 100.8, 112.6, 113.6, 114.3, 116.6, 119.4, 120.9, 126.0, 130.8, 131.7, 132.0, 144.4, 145.6, 147.5, 151.9, 161.5, 192.0; Anal calcd. for $C_{21}H_{16}N_2O_3S$: C, 67.00; H, 4.28; N, 7.44; Found: C, 66.84; H, 4.15; N, 7.32.

12-(3-Nitro-phenyl)-2,3,4,12-tetrahydro-benzo[4,5]thiazolo [2,3-b]quinazolin-1-one ***(4g)***

IR ν_{max} (cm^{-1}, KBr): 3311, 2965, 1721, 1600, 1520, 1351, 751; ^1H NMR ($CDCl_3$, TMS, 400 MHz) δ: 1.94–2.05 (m, 2H), 2.41–2.47 (m, 2H), 2.56–2.67 (m, 2H), 5.45 (s, 1H, ArCH), 7.10–7.56 (m, 4H, Ar–H), 7.68–8.00 (m, 4H, Ar–H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 19.9, 33.4, 37.1, 52.6, 114.2, 115.5, 119.0, 121.7, 122.2, 125.9, 129.0, 130.2, 131.8, 132.7, 143.5, 144.6, 148.3, 151.6, 163.0, 192.7; Anal calcd. for $C_{20}H_{15}N_3O_3S$: C, 63.65; H, 4.01; N, 11.13; Found: C, 63.46; H, 3.89; N, 11.01.

12-(4-Methyl-phenyl)-2,3,4,12-tetrahydro-benzo-[4,5]-thiazolo-[2,3-b]-quinazolin-1-one ***(4h)***

IR ν_{max} (cm^{-1}, KBr): 3336, 2941, 1722, 1637, 1603, 1372, 752; ^1H NMR ($CDCl_3$, TMS, 400 MHz) δ: 1.98–2.05 (m, 2H), 2.28 (s, 3H, CH_3), 2.35–2.47 (m, 2H), 2.54–2.65 (m, 2H), 5.41 (s, 1H, ArCH), 6.95–7.06 (m, 4H, Ar–H), 7.12–7.78 (m, 4H, Ar–H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 20.1, 20.9, 33.5, 40.5, 50.3, 113.2, 116.5, 119.1, 126.3, 128.9, 130.3, 134.6, 138.7, 144.3, 151.6, 166.0, 192.0; Anal calcd. for $C_{21}H_{18}N_2OS$: C, 72.80; H, 5.24; N, 8.09; Found: C, 72.64; H, 5.05; N, 7.93.

12-(4-Dimethylamino-phenyl)-3,3-dimethyl-2,3,4,12-tetrahydro-benzo[4,5]thiazolo[2,3-b]quinazolin-1-one ***(4i)***

IR ν_{max} (cm^{-1}, nujol): 3367, 2950, 1694, 1642, 1540, 1377, 1236, 753; ^1H NMR ($CDCl_3$, TMS, 400 MHz) δ: 1.96–2.02 (m, 2H), 2.26–2.38 (m, 2H), 2.52–2.60 (m, 2H), 3.05 (s, 6H, 2 × CH_3), 5.38 (s, 1H, ArCH), 6.76–6.94 (m, 4H, Ar–H), 7.12–7.40 (m, 4H, Ar–H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 19.6, 27.8, 32.5, 46.3, 49.8, 112.6, 115.7, 118.2, 119.7, 124.5, 128.0, 129.6, 129.8, 130.7, 137.5, 140.5, 145.3, 161.2, 192.4; Anal calcd. for $C_{22}H_{21}N_3OS$: C, 70.37; H, 5.64; N, 11.19; Found: C, 70.13; H, 5.50; N, 11.06.

3,3-Dimethyl-12-phenyl-2,3,4,12-tetrahydro-benzo[4,5]thiazolo[2,3-b]quinazolin-1-one ***(4j)***

IR ν_{max} (cm^{-1}, KBr): 3024, 2962, 1594, 1374, 1249, 777; ^1H NMR ($CDCl_3$, TMS, 400 MHz) δ: 1.07 (s, 6H, 2 × CH_3), 2.36 (s, 2H), 2.31 (AB-q J = 16.48 Hz, 2H, CH_2), 5.51 (s, 1H, ArCH), 7.06–7.16 (m, 5H, Ar–H), 7.22–7.58 (m, 4H, Ar–H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 17.5, 27.3, 29.6, 46.4, 47.0, 53.4, 112.6, 115.5, 119.1, 125.8, 126.7, 127.1, 128.2, 130.0, 130.7, 140.7, 145.4, 162.6, 190.5; Anal calcd. for $C_{22}H_{20}N_2OS$: C, 73.30; H, 5.59; N, 7.77; Found: C, 73.12; H, 5.41; N, 7.63.

3,3-Dimethyl-12-(thiophen-2-yl)-2,3,4,12-tetrahydro-benzo [4,5]thiazolo[2,3-b]quinazolin-1-one ***(4k)***

IR ν_{max} (cm^{-1}, nujol): 2958, 2638, 1594, 1376, 1261, 733; ^1H NMR ($CDCl_3$, TMS, 400 MHz) δ: 1.08 (s, 6H, 2 × CH_3), 2.35 (s, 2H), 3.69 (AB-q J = 20.84 Hz, 2H, CH_2), 5.61 (s, 1H, ArCH), 6.61–7.09 (m, 3H, thienyl), 7.30–7.54 (m, 4H, Ar–H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 17.4, 26.7, 30.0, 46.2, 46.9, 53.4, 112.6, 115.9, 119.1, 123.5, 124.5, 126.0, 126.3, 128.3, 131.2, 139.4, 143.6, 151.7, 166.0, 189.9; Anal calcd. for $C_{20}H_{18}N_2OS_2$: C, 65.54; H, 4.95; N, 7.64; Found:

C, 65.40; H, 4.82; N, 7.49.

12-(2-Hydroxy-phenyl)-3,3-dimethyl-2,3,4,12-tetrahydro-benzo[4,5]thiazolo[2,3-b]quinazolin-1-one ***(4l)***

IR ν_{max} (cm^{-1}, nujol): 3180, 2953, 1642, 1593, 1375, 1260, 755; ^1H NMR ($CDCl_3$, TMS, 400 MHz) δ: 0.97 (s, 6H, 2 × CH_3), 2.31 (s, 2H), 3.71 (AB-q J = 22.0 Hz, 2H, CH_2), 4.71 (br s, 1H, OH), 6.70 (s, 1H, ArCH), 7.13–7.30 (m, 4H, Ar–H), 7.49–7.55 (m, 4H, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 17.6, 27.1, 29.1, 41.4, 45.4, 53.9, 110.9, 115.6, 116.4, 118.2, 120.8, 126, 127.4, 127.9, 129.5, 130.0, 131.2, 145.6, 150.8, 154.5, 166.8, 196.5; Anal calcd. for $C_{22}H_{20}N_2O_2S$: C, 70.19; H, 5.35; N, 7.44; Found: C, 70.03; H, 5.23; N, 7.30.

3,3-Dimethyl-12-(naphthalen-1-yl)-2,3,4,12-tetrahydro-benzo[4,5]thiazolo[2,3-b]quinazolin-1-one ***(4m)***

IR ν_{max} (cm^{-1}, KBr): 3100, 1645, 1470, 1177, 1126, 752; ^1H NMR ($CDCl_3$, TMS, 400 MHz) δ: 1.07 (s, 6H, 2 × CH_3), 2.34 (s, 2H), 3.46 (AB-q J = 23.52 Hz, 2H, CH_2), 6.14 (s, 1H, ArCH), 7.08–7.36 (m, 4H, Ar-H), 7.49–8.09 (m, 7H, Ar–H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 17.6, 27.9, 30.9, 46.6, 51.8, 56.2, 109.9, 116.9, 117.6, 123.8, 124.6, 124.7, 125.1, 126.5, 126.6, 128.2, 128.7, 130.7, 132.5, 133.4, 134.0, 147.8, 149.6, 167.5, 196.8; Anal calcd. for $C_{26}H_{22}N_2OS$: C, 76.07; H, 5.40; N, 6.82; Found: C, 75.93; H, 5.24; N, 6.66.

3,3-Dimethyl-12-styryl-2,3,4,12-tetrahydro-benzo[4,5]thiazolo[2,3-b]quinazolin-1-one ***(4n)***

IR ν_{max} (cm^{-1}, KBr): 3445, 2956, 1622, 1455, 1391, 1238, 751; ^1H NMR ($CDCl_3$, TMS, 400 MHz) δ: 0.99 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 2.30 (AB-q J = 16.38 Hz, 2H, CH_2), 2.48 (s, 2H), 6.02 (m, 1H, ArCH), 7.11 (m, 1H), 7.16 (d, 1H, J = 14.6 Hz), 7.29–7.58 (m, 9H, Ar–H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 18.4, 28.3, 29.6, 42.7, 49.8, 55.0, 111.8, 113.2, 117.2, 123.4, 126.0, 126.4, 127.4, 127.7, 128.2, 128.8, 130.5, 138.2, 142.4, 149.5, 165.3, 197.0; Anal calcd. for $C_{24}H_{22}N_2OS$: C, 74.58; H, 5.74; N, 7.25; Found: C, 74.42; H, 5.64; N, 7.13.

12-(2-Hydroxy-3-methoxy-phenyl)-3,3-dimethyl-2,3,4,12-tetrahydro-benzo[4,5]thiazolo[2,3-b]quinazolin-1-one ***(4o)***

IR ν_{max} (cm^{-1}, KBr): 3385, 3199, 2953, 1641, 1584, 1540, 1381, 1229, 757; ^1H NMR ($CDCl_3$, TMS, 400 MHz) δ: 0.96 (s, 6H, 2 × CH_3), 2.34 (s, 2H), 2.58 (AB-q J = 18.16 Hz, 2H, CH_2), 3.86 (s, 3H, OCH_3), 5.78 (s, 1H, ArCH), 6.55–6.92 (m, 3H, Ar–H), 7.13–7.52 (m, 4H, Ar–H), 9.90 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 18.6, 27.1, 29.1, 41.5, 45.0, 55.8, 56.0, 110.3, 113.5, 116.7, 119.0, 120.8, 122.2, 126.0, 130.0, 130.3, 131.1, 142.2, 145.6, 148.7, 151.4, 161.1, 197.0; Anal calcd. for $C_{23}H_{22}N_2O_3S$: C, 67.96; H, 5.46; N, 6.89; Found: C, 67.77; H, 5.26; N, 6.76.

12-(4-Bromo-phenyl)-3,3-dimethyl-2,3,4,12-tetrahydro-benzo[4,5]thiazolo[2,3-b]quinazolin-1-one ***(4p)***

IR ν_{max} (cm^{-1}, nujol): 2961, 2928, 1701, 1593, 1487, 1373, 1242, 734; ^1H NMR ($CDCl_3$, TMS, 400 MHz) δ: 1.06 (s, 6H, 2 × CH_3), 2.36 (s, 2H), 4.09 (AB-q J = 20.52 Hz, 2H, CH_2), 5.42 (s, 1H, ArCH), 6.92–7.12 (m, 4H, Ar–H), 7.33–7.73 (m, 4H, Ar–H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 19.7, 27.2, 28.3, 46.3, 49.8, 112.3, 115.1, 118.1, 120.8, 126.0, 129.6, 130.0, 130.8, 131.1, 137.2, 143.3, 150.4, 165.0, 191.0; Anal calcd. for $C_{22}H_{19}N_2BrOS$: C, 60.14; H, 4.36; N, 6.38; Found: C, 60.03; H, 4.20; N, 6.26.

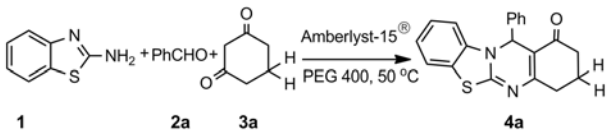
12-(3-Hydroxy-phenyl)-3,3-dimethyl-2,3,4,12-tetrahydro-benzo[4,5]thiazolo[2,3-b]quinazolin-1-one ***(4q)***

IR ν_{max} (cm^{-1}, nujol): 3320, 2960, 1718, 1642, 1581, 1376, 1248, 756; ^1H NMR ($CDCl_3$, TMS, 400 MHz) δ: 1.04 (s, 6H, 2 × CH_3), 2.32 (s, 2H), 3.48 (AB-q J = 18.24 Hz, 2H, CH_2), 5.36 (s, 1H, ArCH), 6.45–6.74 (m, 4H, Ar–H), 6.96–7.42 (m, 4H, Ar–H), 9.64 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 18.6, 28.5, 36.7, 48.5, 52.4, 110.7, 112.6, 114.7, 116.2, 118.3, 118.9, 124.8, 129.7, 131.2, 132.3, 139.6, 144.5, 147.2, 156.8, 160.2, 190.4; Anal calcd. for $C_{22}H_{20}N_2O_2S$: C, 70.19; H, 5.35; N, 7.44; Found: C, 70.02; H, 5.20; N, 7.26.

3 Results and discussions

In order to achieve the most suitable conditions for the present reaction, we first investigated the model reaction using 1 equiv each of 2-aminobenzothiazole **1**, benzaldehyde **2a** and cyclohexane-1,3-dione **3a**. These were stirred at ambient temperature in ethanol. The reaction did not proceed to completion even after 10 h with only 36% of the product **4a** being isolated. In order to improve the yield and optimize the reaction conditions, the same reaction was carried out in the presence of Amberlyst-15® catalyst under similar conditions. Surprisingly, a significant improvement was observed and the yield of the product **4a** was enhanced to 70% after stirring the reaction mixture for 3 h. To further enhance the yield, we chose PEG 400 as solvent for the model reaction and achieved 92% isolated yield in 30 min at 50 °C (Scheme 1).

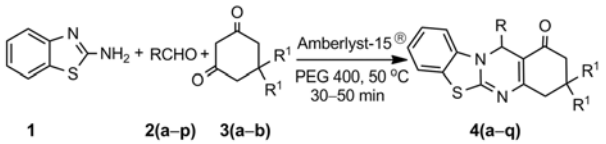
Next, we optimized the catalyst loading for this reaction and we noted that although the product could be formed with low catalyst loading (20 mg/mmol of the reactant), the best outcome, in terms of yield and the reaction time, was obtained with 100 mg/mmol of Amberlyst-15® (Table 1).



Scheme 1 Optimized reaction conditions of the model reaction for the synthesis of benzothiazolo-[2,3-*b*]-quinazolinones.

We also examined the effect of temperature on this reaction (Figure 1). It was found that the optimum temperature was 50 °C from the point of view of yield and reaction time. At higher temperatures, no further improvement on yield and reaction time was observed. On the other hand, the reaction did not proceed at room temperature. At 50 °C, the reaction proceeded smoothly and almost complete conversion of the reagent was observed. Also, the model reaction was carried out in various solvents commonly used in organic synthesis (Table 2) and the best result was obtained in solvent PEG 400 at 50 °C.

The scope and generality of this three-component, one-pot synthesis of benzothiazolo-[2,3-*b*]-quinazolin-1-one erivatives are well illustrated with structurally diverse aldehydes (Scheme 2) and the results are summarized in Table 3. The reaction proceeded smoothly and equally well for electron-withdrawing as well as electron-donating aldehydes to afford the corresponding benzothiazolo-[2,3-*b*]-quinazolinones in good to excellent yields.



Scheme 2 Synthesis of benzothiazolo-[2,3-*b*]-quinazolin-1-ones via multi-component reaction.

Table 1 Optimization of the amount of the catalyst [a)]

Entry	Catalyst (mg)	Time (min)	Yield (%) [b)]
1	20	420	58
2	40	270	67
3	60	240	74
4	80	120	80
5	100	30	92

a) Reaction conditions: 2-Aminobenzothiazole **1** (1 mmol), benzaldehyde **2a** (1 mmol), cyclohexane-1,3-dione **3a** (1 mmol); catalyst: Amberlyst-15® (mg); temp: 50 °C; solvent : PEG (2 mL). b) Isolated yields.

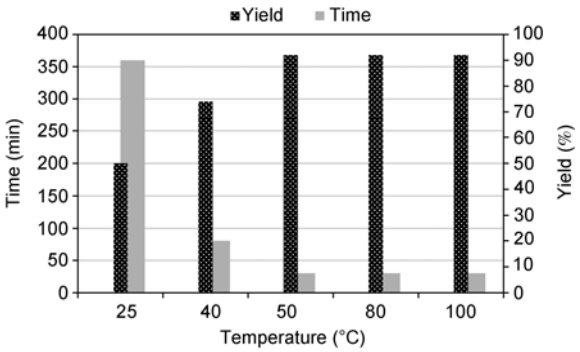


Figure 1 Effect of temperature on the synthesis of benzothiazolo-[2,3-*b*]quinazoline-1-ones. Reaction conditions: 2-Aminobenzothiazole **1** (1 mmol), benzaldehyde **2a** (1 mmol), cyclohexane-1,3-dione **3a** (1 mmol); catalyst: Amberlyst-15® (100 mg); temp: (°C); solvent: PEG 400 (2 mL). b) Isolated yields.

Table 2 Effect of solvents on the synthesis of benzothiazolo-[2,3-*b*] quinazoline-1-ones[a)]

S.No.	Solvent (mL)	Time (min)	Yield (%) [b)]
1	MeOH	50	78
2	EtOH	50	80
3	THF	90	70
4	CH_3CN	45	78
5	toluene	180	65
6	PEG 200	35	92
7	PEG 400	30	92
8	DMF	200	60

a) Reaction conditions: 2-Aminobenzothiazole **1** (1 mmol), benzaldehyde **2a** (1 mmol), cyclohexane-1,3-dione **3a** (1 mmol); catalyst: Amberlyst-15® (100 mg); temp: 50 °C; solvent: 2 mL. b) Isolated yields.

We also investigated the recyclability of the catalyst system (Amberlyst-15® in PEG 400) (Table 4). The model reaction was carried out under the optimized conditions. After complete conversion of the starting materials, the reaction mixture was cooled in dry-ice acetone bath to precipitate the PEG 400 and was extracted with ether (PEG being insoluble in ether). The ether layer was decanted, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to produce the products. The PEG 400 phase along with resin was used as such for subsequent runs (four runs) with fresh substrates under the same conditions. The recycled catalyst and solvent exhibited excellent recyclability in this reaction as the reaction time and yield remained almost the same.

As far as the mechanism of the above transformation (Scheme 2) is concerned, a reasonable possibility is proposed in Scheme 3. The reaction presumably proceeds via two steps: reaction of aldehyde **2(a–p)** and cyclic β-diketone **3(a–b)** by Knoevenagel condensation to produce α,β-unsaturated ketone (**5**), which then could undergo Michael-type addition reaction with 2-aminobenzothiazole (**1**) to form an adduct (**6**). The adduct formed could then be cyclized intramolecularly to give (**7**) which could then lose water to afford tetraheterocyclic benzothiazolo-[2,3-*b*]-quinazolin-1-one ring systems **4(a–q)**. The asymmetric aspect of the reaction, i.e.; the regioselectivity of the reaction is confirmed by theoretical studies according to which the endocyclic nitrogen is more nucleophilic as compared to the exocyclic amino group. Thus, the possibility of formation of isomeric product *via* nucleophilic attack of exocyclic amino group is completely eliminated [12].

4 Conclusion

In summary, Amberlyst-15® has been demonstrated as an efficient and environmentally benign catalyst for the multi-component synthesis of benzothiazolo-[2,3-*b*]-quinazolin-1-ones. This protocol further demonstrates the values of PEG-promoted synthesis in avoiding hazardous organic

Table 3 Amberlyst-15® mediated synthesis of benzothiazolo-[2,3-*b*]-quinazolin-1-ones [a)]

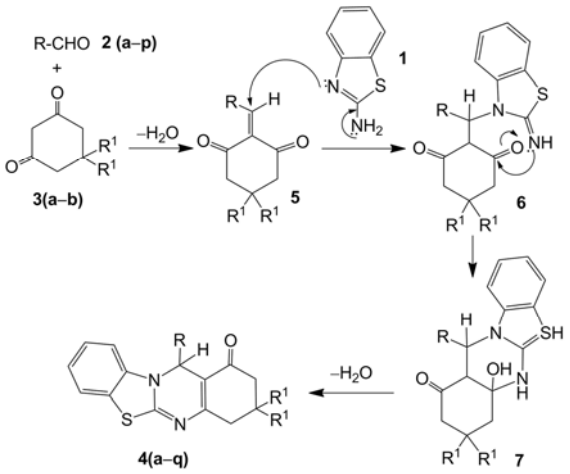
Entry	R	R^1	Product	M.P. (°C)	Time (min)	Yield (%) [b)]
1	C_6H_5	H	**4a**	230–234 [24]	30	92
2	4-Cl-C_6H_4	H	**4b**	212–214	30	92
3	4-MeO-C_6H_4	H	**4c**	186–190	30	92
4	4-HO-C_6H_4	H	**4d**	224–228	30	90
5	4-NO_2-C_6H_4	H	**4e**	218–222	45	90
6	piperonyl	H	**4f**	216–220	30	88
7	3-NO_2-C_6H_4	H	**4g**	160–164	40	90
8	4-Me-C_6H_4	H	**4h**	146–150	30	92
9	4-$(CH_3)_2$N-C_6H_4	H	**4i**	250–252	45	90
10	C_6H_5	CH_3	**4j**	224–226 [25]	30	92
11	2-thienyl	CH_3	**4k**	134–138	40	89
12	2-HO-C_6H_4	CH_3	**4l**	166–170	30	92
13	1-naphthyl	CH_3	**4m**	286–290	50	87
14	cinnamyl	CH_3	**4n**	164–168	40	88
15	2-HO-3-MeO-C_6H_3	CH_3	**4o**	168–172	35	85
16	4-Br-C_6H_4	CH_3	**4p**	176–180	35	92
17	3-HO-C_6H_4	CH_3	**4q**	234–236	40	91

a) Reaction conditions: 2-Aminobenzothiazole **1** (1 mmol), aldehyde **2(a–p)** (1 mmol), cyclic β-diketone **3(a–b)** (1 mmol); catalyst: Amberlyst-15® (100 mg); temp: 50 °C; solvent: PEG 400 (2 mL). b) Isolated yields.

Table 4 Recycling studies of the catalyst system [a)]

No. of cycles [a)]	Fresh	Run 1	Run 2	Run 3	Run 4
Yield (%) [b)]	92	92	92	91	90
Time (min)	30	30	30	30	30

a) Reaction conditions: 2-Aminobenzothiazole **1** (1 mmol)**,** benzaldehyde **2a** (1 mmol), cyclohexan-1,3-dione **3a** (1 mmol); catalyst: Amberlyst-15® (100 mg); temp: 50 °C; solvent: PEG 400 (2 mL). b) Isolated yields.



Scheme 3 Proposed mechanism for the synthesis of benzothiazolo-[2,3-*b*]-quinazolinones.

solvents and toxic catalysts, increasing yields, reducing reaction time, and streamlining high-throughput chemistry. The mildness, experimental convenience, compatibililty with a variety of functional groups and reusability of the catalyst as well as the solvent are also the key advantages which make this method a superior alternative to the existing protocols.

The author (Ritika Chauhan) is thankful to the UGC (University Grants Commission) for providing the junior research fellowship and also to the Director of University Science and Instrumentation Centre, University of Delhi, Delhi for providing the spectral analysis data.

1 Zhu J, Bienaymé H. *Multicomponent Reactions*. Wiley-VCH: Weinheim, 2005

2 (a) Weber L. Multi-component reactions and evolutionary chemistry. *Drug Disc Today*, 2002, 7(2): 143–147; (b) Domling A. Recent advances in isocyanide-based multicomponent chemistry. *Curr Opin Chem Biol*, 2002, 6: 306–313; (c) Domling A. The discovery of new isocyanide-based multi-component reactions. *Curr Opin Chem Biol*, 2002, 4: 318–323

3 (a) Orru RVA, de Greef M. Recent advances in solution-phase multicomponent methodology for the synthesis of heterocyclic compounds. *Synthesis*, 2003, (10): 1471–1499; (b) Balme G, Bossharth E, Monteiro N. Pd-assisted multicomponent synthesis of heterocycles. *Eur J Org Chem*, 2003, 4101–4111; (c) Brase S, Gil C, Knepper K. The recent impact of solid-phase synthesis on medicinally relevant benzoannelated nitrogen heterocycles. *Bioorg Med Chem*, 2002, 10: 2415–2437; (d) Domling A, Ugi I. Multicomponent reactions with isocyanides. *Angew Chem Int Ed*, 2000, 39: 3168–3210

4 (a) McClenaghan ND, Passalacqua R, Loiseau F, Campagna S, Verheyde B, Hameurlaine A, Dehaen W. Ruthenium(II) dendrimers containing carbazole-based chromophores as branches. *J Am Chem Soc*, 2003, 125: 5356–5365; (b) Jian H, Tour JM. En route to surface-bound electric field-driven molecular motors. *J Org Chem*, 2003, 68: 5091–5103; (c) Cherng SC, Huang WH, Shiau CY, Lee AR, Chou TC. Mechanisms of antiplatelet activity of PC-09, a newly synthesized pyridazinone derivative. *Eur J Pharmacol*, 2006, 532: 32–37

5 (a) Witt A, Bergman J. Recent developments in the field of quinazoline chemistry. *Curr Org Chem*, 2003, 7: 659–677; (b) Connolly DJ, Cusack D, O'Sullivan TP, Guiry PJ. Synthesis of quinazolinones and quinazolines. *Tetrahedron*, 2005, 61: 10153–10202; (c) Michael JP. Quinoline, quinazoline and acridone alkaloids. *Nat Prod Rep*, 1999, 16: 697–709; (d) Michael JP. Quinoline, quinazoline and acridone alkaloids. *Nat Prod Rep*, 2002, 19: 742–760; (d) Michael JP. Quinoline, quinazoline and acridone alkaloids. *Nat Prod Rep*, 2003, 20: 476–493

6 Grasso S, Micale N, Monforte AM, Monforte P, Polimeni S, Zappala M. Synthesis and *in vitro* antitumour activity evaluation of 1-aryl-1*H*,3*H*-thiazolo[4,3-*b*]quinazolines. *Eur J Med Chem*, 2000, 35:

1115–1119
7 (a) Testard A, Picot L, Lozach O, Blairvacq M, Meijer L, Murillo L, Piot JM, Thie´ry V, Besson T. Synthesis and evaluation of the anti-proliferative activity of novel thiazoloquinazolinone kinases inhibitors. *J Enzym Inhib Med Chem*, 2005, 20(6): 557–568; (b) Testard A, Loge C, Leger B, Robert JM, Lozach O, Blairvacq M, Meijer L, Thiéry V, Besson T. Thiazolo[5,4-*f*]quinazolin-9-ones, inhibitors of glycogen synthase kinase-3. *Bioorg Med Chem Lett*, 2006, 16: 3419–3423
8 Shaabani A, Rahmati A, Naderi S. A novel one-pot three-component reaction: Synthesis of triheterocyclic 4*H*-pyrimido[2,1-*b*]benzazoles ring systems. *Bioorg Med Chem Lett*, 2005, 15: 5553–5557
9 Trapani G, Franco M, Latrofa A, Carotti A, Genchi G, Serra M, Biggio G, Liso G. Synthesis and benzodiazepine receptor binding of some imidazo and pyrimido[2,1-*b*]benzothiazoles. *Eur J Med Chem*, 1996, 31: 575–587
10 Pingle MS, Vartale SP, Bhosale VN, Kuberkar SV. A convenient synthesis of 3-cyano-4-imino-2-methylthio-4*H*-pyrimido-[2,1-*b*] [1,3] benzothiazole and its reactions with selected nucleophiles. *ARKIVOC*, 2006, 10: 190–198
11 Trapani G, Franco M, Latrofa A, Genchi G, Iacobazzi V, Ghiani CA, Maciocco E, Liso G. Synthesis and benzodiazepine receptor binding of some imidazo-, pyrimido[2,1-*b*]benzoxazoles and pyrimido[1,2-*a*]benzimidazoles. *Eur J Med Chem*, 1997, 32: 83–89
12 Sharma BK, Sharma PK, Kumar M. One-pot, multicomponent sequential synthesis of benzothiazoloquinazolinones. *Synth Commun*, 2010, 40(16): 2347–2352
13 Dake SA, Tekale SU, Sarda SR, Jadhav WN, Bhusare SR, Pawar RP. Anhydrous zinc chloride: An efficient catalyst for one pot synthesis of 2,3,4,12-tetrahydro-benzo-[4,5]-thiazolo-[2,3-*b*]-quinazolin-1-ones. *ARKIVOC*, 2008, 17: 241–247
14 Mourad AFE, Aly AA, Farag HH, Beshr EA. Microwave assisted synthesis of triazoloquinazolinones and benzimidazoquinazolinones. *Beil J Org Chem*, 2007, 3: 11–16
15 (a) Cornlis B, Herrmann WA, Muhler M, Wong CH. *Catalysis from A to Z: A Concise Encyclopedia*. Wiley-VCH: Weinheim, 2007. 1–3; (b) Sheldon R, Arends L, Hanefeld U. *Green Chemistry and Catalysis*. Wiley-VCH: Weinheim, 2007
16 (a) Lee SH, Park DR, Kim H, Lee JH, Jung JC, Woo SY, Song WS, Kwon MS, Song IK. Direct preparation of dichloropropanol (DCP) from glycerol using heteropolyacid (HPA) catalysts: A catalyst screen study. *Catal Commun*, 2008, 9: 1920–1923; (b) Park S, Cho KM, Youn MH, Seo JG, Baeck SH, Kim TJ, Chung YM, Oh SH, Song IK. Epoxidation of propylene with hydrogen peroxide over TS-1 catalyst synthesized in the presence of polystyrene. *Catal Lett*, 2008, 122: 349–353; (c) Song IK, Lee WY. Heteropolyacid (HPA)-polymer composite films as heterogeneous catalysts and catalytic membranes. *Appl Catal A: Gen*, 2003, 256: 77–98
17 Kunin R, Meitzner EF, Oline JA, Fisher SA, Frisch N. Characterization of Amberlyst 15 macroreticular sulfonic acid cation exchange resin. *I & EC Prod Res Dev*, 1962, 140–144
18 Alinezhada H, Tajbakhsha M, Mahdavia N. One-pot reductive amination of carbonyl compounds using sodium Borohydride-Amberlyst 15. *Synth Commun*, 2010, 40: 951–956
19 Kumar KS, Iqbal J, Pal M. Amberlyst-15: A mild, efficient and reusable heterogeneous catalyst for *N*-*tert*-butoxycarbonylation of amines. *Tetrahedron Lett*, 2009, 50: 6244–6246
20 Das B, Damodar K, Chowdhury N. Amberlyst-15: A mild, efficient and reusable heterogeneous catalyst for Michael addition of pyrroles to α,β-unsaturated ketones. *J Mol Catal A: Chem*, 2007, 269: 81–84
21 Esteves AP, Silva ME, Rodrigues ML, Oliveira-Camposa AMF, Hrdina R. Aza-Michael reactions with vinyl sulfones and Amberlyst-15 as catalyst. *Tetrahedron Lett*, 2007, 48: 9040–9043
22 (a) Chen J, Spear SK, Huddleston JG, Rogers RD. Polyethylene glycol and solutions of polyethylene glycol as green reaction media. *Green Chem*, 2005, 7: 64–82; (b) Mukhopadhyay C, Tapaswi PK. PEG-mediated catalyst-free expeditious synthesis of 2-substituted benzimidazoles and bis-benzimidazoles under solvent-less conditions. *Tetrahedron Lett*, 2008, 49: 6237–6240; (c) Ballini R, Barboni L, Palmieri A. Improved chemoselective, ecofriendly conditions for the conversion of primary alkyl halides into nitroalkanes under PEG400. *Green Chem*, 2008, 10: 1004–1006
23 (a) Kidwai M, Chauhan R, Jahan A. Efficient CAN catalyzed synthesis of 1*H*-indazolo[1,2-*b*]phthalazine-1,6,11-triones: An eco-friendly protocol. *Chinese Sci Bull*, 2012, 57(18): 2273–2279; (b) Kidwai M, Chauhan R, Bhatnagar D. Eco-friendly synthesis of 2-aminothiazoles using Nafion-H as a recyclable catalyst in PEG-water solvent system. *J Sulf Chem*, 2011, 32(1): 37–44; (c) Kidwai M, Chauhan R. Sulfamic acid: An efficient, cost-effective and recyclable catalyst for the synthesis of triazole[1,2-a] indazole-trione derivatives. *RSC Adv*, 2012, DOI:10.1039/C2RA20662E
24 Pavlenko AA, Shikhaliev Kh S, Potapov AY, Krylsky DV. Three-component reaction of 2-aminobenzothiazole with methylene-active carbonyl compounds and aldehydes. *Chem Heter Comp (New York, United States),* 2005, 41(5): 689–690
25 Shaabani A, Farhangi E, Rahmati A. Synthesis of tetrahydrobenzimidazo[1,2-*b*]quinazolin-1(2*H*)-one and tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolin-8(4*H*)-one ring systems under solvent-free conditions. *Comb Chem High Throughput Screening*, 2006, 9: 771–776