DOI 10.1007/s10593-018-2292-0

Chemistry of Heterocyclic Compounds **2018**, *54*(4), 478–481

Condensation of 2-aminomethylaniline with aldehydes and ketones for the fast one-pot synthesis of a library of 1,2,3,4-tetrahydroquinazolines under flow conditions

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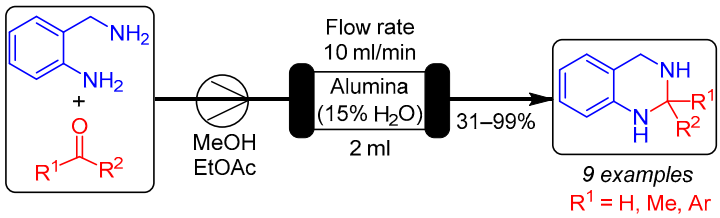
Published in Khimiya Geterotsiklicheskikh Soedinenii, 2018, *54*(4), 478–481

Submitted February 12, 2018
Accepted March 28, 2018



A new eco-friendly and reliable methodology for the synthesis of 1,2,3,4-tetrahydroquinazolines is proposed. This simple protocol was tested for the continuous synthesis of a small library of 1,2,3,4-tetrahydroquinazoline derivatives demonstrating good versatility and applicability.

Keywords: aldehydes, alumina, tetrahydroquinazoline, flow chemistry, green chemistry.

Nitrogen-containing heterocycles represent a significant structural motif widely distributed in biologically active natural and synthetic compounds.[1] Among the others, quinazolines and 1,2,3,4-tetrahydroquinazolines have attracted a large interest from both the synthetic and pharmaceutical points of view. In fact, the quinazoline scaffold is a part of numerous pharmaceutically active compounds (Fig. 1), and in particular, 1,2,3,4-tetrahydro derivatives display anti-inflammatory and analgesic properties.[2]

The quinazoline moiety is easily prepared by 1,2,3,4-tetrahydroquinazoline oxidation,[3] that, in turn, can be obtained in the condensation reaction between 2-aminobenzylamine and aldehydes or ketones. This reaction has been explored by several research groups, the desired product has been obtained for the first time by refluxing the reagents in benzene or xylene with azeotropic removal of water.[4] In order to improve the green aspect of the synthesis, ionic liquids have been explored as reaction medium,[5] and more recently, Scott et al. proposed a protocol which involves "water slurry" or "solvent-free" conditions.[6] It was also demonstrated that 2-aryl-substituted derivatives can exhibit a ring-chain tautomeric equilibrium depending on the nature of the substituent and the solvent.[7] Flow chemistry in the past decades has received a growing attention because of a number of benefits over traditional batch techniques[8] with interesting applications in combinatorial chemistry and library synthesis.[9]

As an extension of our interest in the synthesis of heterocycles,[10] including flow techniques,[11] we optimized the conditions for the fast preparation of a library of substituted 1,2,3,4-tetrahydroquinazoline derivatives using a flow setup.

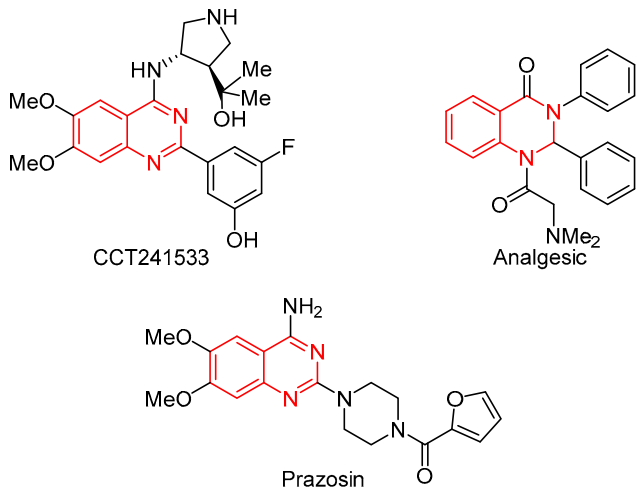


Figure 1. Biologically active quinazoline derivatives.

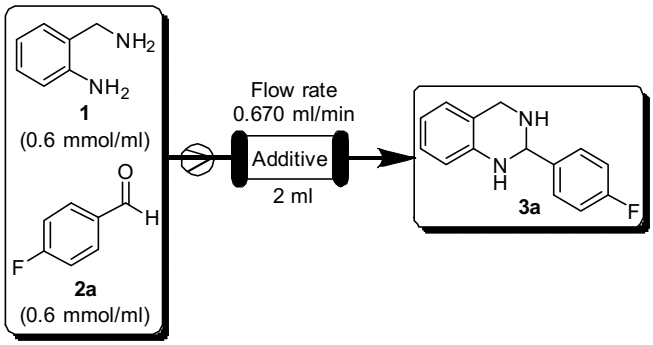


Figure 2. Preliminary reaction condition investigations for the synthesis of compound **3a**.

Table 1. Yield of compound **3a** under different reaction conditions

Entry	Solvent	Additive	Yield*, %
1	EtOAc	Na_2SO_4	23
2	MeOH	Na_2SO_4	28
3	THF	Na_2SO_4	–
4	MeOH–EtOAc, 4:1	Alumina**	>99

* Determined from ^{1}H NMR integrated values and based on the consumption of the aldehyde.
** Grade V (by addition of 15% w/w of water).

The results of a preliminary screening of the reaction conditions, using as model the reaction between diamine **1** and *p*-fluorobenzaldehyde (**2a**) in a 2-ml tubular reactor filled with the promoter of the reaction are summarized in Figure 2 and Table 1.

Considering that the cyclization proceeds as a condensation of the Schiff base intermediate (not shown) we attempted to promote the reaction by removing the water from the passage by a drying agent like sodium sulfate (entries 1–3). It was observed that, in these cases, the solvent used as carrier influenced the outcome of the reaction and the best conversion was obtained in MeOH (28%), in comparison to EtOAc (23%), whereas in THF the ^{1}H NMR of the crude showed the presence of a complex reaction mixture. Despite the very low solubility of the reagents it was reported that the reaction can be conveniently carried out in water and that the reaction times under "water slurry" conditions are, in some cases and depending on the nature of the substituents on the aromatic ring of the aldehydes, similar to those observed in "solvent-free" conditions under gentle heating.[6] Suggesting that, most probably, hydrophobic effects and/or hydrogen bonding could facilitate the reaction affording the desired product in good yield and short reaction time. Entry 4 reports the results obtained when the reactor was filled with alumina grade V, obtained by the addition of 15% w/w of water to neutral alumina. Using these conditions, diamine **1** was converted into 1,2,3,4-tetrahydroquinazoline **3a** in 99% yield after a 3 min residence time and it was demonstrated that flow rate can be increased till obtaining the same conversion yield with a 0.2 min residence time. To reduce the absorption of the products on alumina a polar solvent mixture was used (MeOH–EtOAc, 4:1).

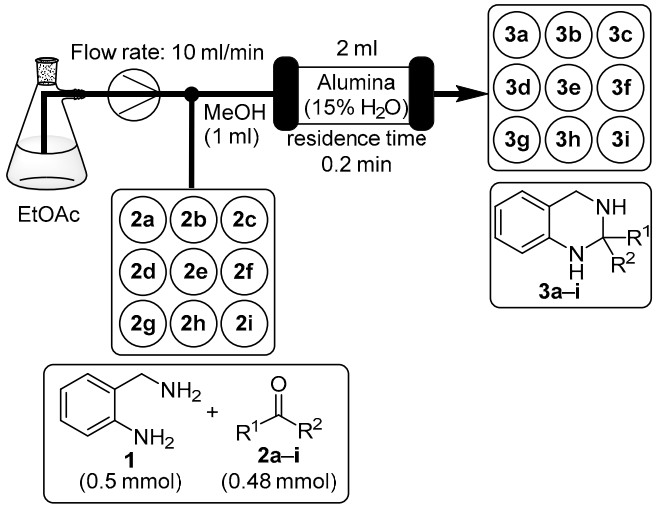


Figure 3. General setup of the experiment for the synthesis of compounds **3a**–**i**.

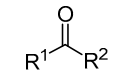
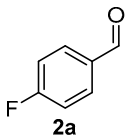
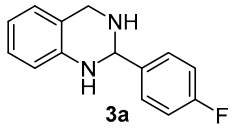
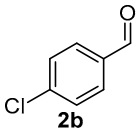
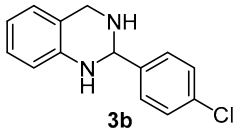
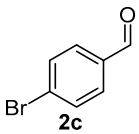
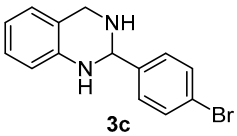
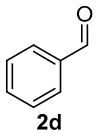
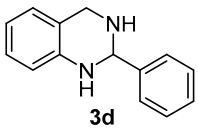
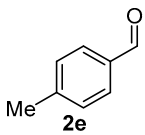
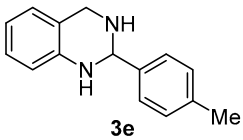
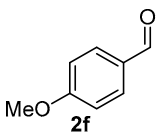
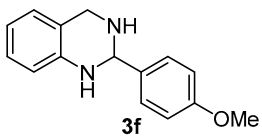
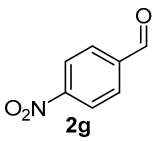
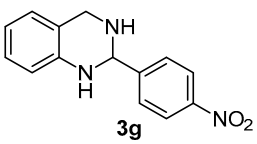
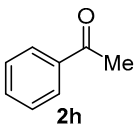
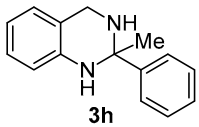
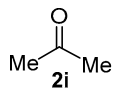
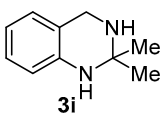
Considering that alumina and water are not consumed during the reaction and that the starting materials were not adsorbed by the column and quantitatively converted into final products we envisioned the possibility to flux sequentially freshly prepared mixture of diamine **1** with different aldehydes **2a**–**g** and ketones **2h**,**i** to prepare a library of 1,2,3,4-tetrahydroquinazolines **3a**–**i** variously substituted at the C-2 atom with aromatic and aliphatic substituents. Instantaneously prepared solutions of equimolar amounts of compounds **1** and **2a–i** in MeOH were injected every 6 min *via* a T-junction in a stream of EtOAc generated with a variable speed FMI-LAB pump and fluxed through a 2-ml tubular reactor filled with alumina grade V collecting 30 ml of solvent after each injection (Fig. 3).

Considering that in these conditions the reaction is very fast, a flow rate of 10 ml/min (corresponding to 0.2 min residence time) was applied enabling a very rapid preparation of the desired library of compounds **3a**–**i**.

The results obtained exploring the scope of the reaction are collected in Table 2 evidencing an excellent efficiency of the protocol with aldehydes containing both electron-withdrawing and electron-donating groups (entries 1–7). Moderate to good results were obtained using ketones (entries 8, 9), as a consequence of the reduced reactivity of the carbonyl derivative affording lower conversion yields. In comparison to the results reported in literature,[6] the reaction promoted by alumina grade V in our flow conditions is considerably faster than the same reaction performed under "water slurry" or "solvent-free" conditions. This is particularly evident in substrates having strong and weak electron-withdrawing group. As an example, compounds **3c**,**g** can be prepared under "water slurry" conditions with 99 and 90% conversion but in 3 and 18 h, respectively.[6,7]

This indicates that alumina has an active role in the catalysis of the reaction probably in both steps of the known mechanism: activating the C=O bond and removing water during the formation of the Schiff base and

Table 2. Yields of compounds **3a**–**i** in the continuous flow experiment

Entry		Product	Yield*, %
1	 **2a**	 **3a**	>99
2	 **2b**	 **3b**	>99
3	 **2c**	 **3c**	>99
4	 **2d**	 **3d**	>99
5	 **2e**	 **3e**	>99
6	 **2f**	 **3f**	>99
7	 **2g**	 **3g**	>99
8	 **2h**	 **3h**	31
9	 **2i**	 **3i**	89

* Determined from ^{1}H NMR integrated values and based on consumption of compounds **2a**–**i** or **1** (entries 8 and 9). The NMR analysis evidenced a tautomeric equilibrium as reported in the literature.[7]

facilitating the tautomerism toward the formation of the cyclic form.

In conclusion, we have demonstrated that simple flow setup allows preparation of the library of 2-substituted 1,2,3,4-tetrahydroquinazolines in a fast, clean, and efficient manner. The methodology is suitable for the combinatorial approach in the synthesis of biologically active compounds and can be, in theory, further improved by the automatization of the entire process. This will be the subject for the future investigations.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on Bruker DPX 200 (200 and 50 MHz, respectively) and Bruker DRX spectrometers (400 and 101 MHz, respectively) at 25°C in $CDCl_3$, using TMS as internal standard. Melting points were measured on a Reichert Kofler Hot Bench apparatus and are uncorrected.

All the starting materials were commercially available. Solvents and reagents were used as received unless otherwise noted.

Synthesis of compounds 3a–**i** (General flow experiment setup). In a continuous system equipped with a FMI Lab-Pump model RP-SY pump and a 2-ml tubular reactor charged with deactivated alumina (15% w/w H_2O), EtOAc is fluxed with a rate of 10 ml/min. Freshly prepared solutions of (2-aminobenzyl)amine **1** (0.061 g, 0.5 mmol) and aldehydes **2a**–**g** or ketones **2h**,**i** (0.48 mmol) in MeOH (1 ml) were sequentially injected by a syringe in the EtOAc stream through a septum of a three-way connector. The products were collected sequentially in test tubes and evaporated under reduced pressure affording the corresponding quinazolines **3a**–**i**. Physical properties of the compounds are in good correlation with the literature data.[6,7,12]

2-(4-Fluorophenyl)-1,2,3,4-tetrahydroquinazoline (3a).[7] Yield 93 mg (85%), white crystals, mp 93–96°C (mp 95–97°C[7]). ^{1}H NMR spectrum (200 MHz), δ, ppm (*J*, Hz): 7.55–7.48 (2H, m, H Ar); 7.14–7.05 (3H, m, H Ar); 6.97 (1H, d, *J* = 7.3, H Ar); 6.76 (1H, t, *J* = 7.1, H Ar); 6.61 (1H, d, *J* = 7.9, H Ar); 5.24 (1H, s, CH); 4.27 (1H, d, *J* = 16.7, CH_2); 4.25 (1H, br. s, NH); 3.98 (1H, d, *J* = 16.7, CH_2); 2.00 (1H, br. s, NH). ^{13}C NMR spectrum (50 MHz), δ, ppm (*J*, Hz): 162.7 (d, *J* = 246); 143.6; 137.5; 128.4 (d, *J* = 8); 127.4; 126.3; 121.2; 118.4; 115.6 (d, *J* = 20); 115.1; 68.9; 46.3.

2-(4-Chlorophenyl)-1,2,3,4-tetrahydroquinazoline (3b).[7] Yield 62 mg (53%), pale-yellow crystals, mp 89–91°C (mp 88–90°C[7]). ^{1}H NMR spectrum (200 MHz), δ, ppm (*J*, Hz): 7.49 (2H, d, *J* = 8.4, H Ar); 7.38 (2H, d, *J* = 8.5, H Ar); 7.08 (1H, dd, *J* = 7.9, *J* = 7.3, H Ar); 6.96 (1H, d, *J* = 7.3, H Ar); 6.75 (1H, t, *J* = 7.3, H Ar); 6.62 (1H, d, *J* = 7.9, H Ar); 5.26 (1H, s, CH); 4.25 (1H, d, *J* = 16.7, CH_2); 4.24 (1H, br. s, NH); 3.98 (1H, d, *J* = 16.7, CH_2); 3.97 (1H, br. s, NH). ^{13}C NMR spectrum (50 MHz), δ, ppm: 143.8; 140.5; 134.6; 128.7; 128.5; 127.8; 126.7; 121.7; 118.8; 115.6; 69.3; 46.6.

2-(4-Bromophenyl)-1,2,3,4-tetrahydroquinazoline (3c).[6] Yield 86 mg (62%), pale-yellow crystals, mp 82–84°C (mp 82.2–84.9°C[6]) ^{1}H NMR spectrum (200 MHz), δ, ppm (*J*, Hz): 7.54 (2H, d, *J* = 8.3, H Ar); 7.42 (2H, d, *J* = 8.4,

H Ar); 7.08 (1H, t, *J* = 7.5, H Ar); 6.96 (1H, d, *J* = 7.4, H Ar); 6.75 (1H, t, *J* = 7.3, H Ar); 6.61 (1H, d, *J* = 7.9, H Ar); 5.23 (1H, s, CH); 4.24 (1H, d, *J* = 16.8, CH_2); 4.19 (1H, br. s, NH); 3.96 (1H, d, *J* = 16.7, CH_2); 2.0 (1H, br. s, NH). ^{13}C NMR spectrum (50 MHz), δ, ppm: 143.3; 140.6; 131.8; 128.4; 127.4; 126.2; 122.4; 121.3; 118.4; 115.1; 68.9; 46.1.

2-Phenyl-1,2,3,4-tetrahydroquinazoline (3d).[7] Yield 42 mg (42%), pale-yellow crystals, mp 99–101°C (mp 98–101°C[7]). ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 7.56–7.54 (2H, m, H Ar); 7.45–7.36 (3H, m, H Ar); 7.09 (1H, t, *J* = 7.6, H Ar); 6.93 (1H, d, *J* = 7.3, H Ar); 6.75 (1H, t, *J* = 7.3, H Ar); 6.62 (1H, d, *J* = 7.9, H Ar); 5.25 (1H, s, CH); 4.30 (1H, d, *J* = 16.7, CH_2); 4.25 (1H, br. s, NH); 4.03 (1H, d, *J* = 16.7, CH_2); 2.0 (1H, br. s, NH). ^{13}C NMR spectrum (101 MHz), δ, ppm: 144.2; 142.0; 129.2; 129.0; 127.7; 127.1; 126.7; 121.7; 118.6; 115.5; 70.0; 46.9.

2-(4-Methylphenyl)-1,2,3,4-tetrahydroquinazoline (3e).[12] Yield 72 mg (67%), white crystals, mp 95–96°C (mp 105–107°C[12]). ^{1}H NMR spectrum (200 MHz), δ, ppm (*J*, Hz): 7.43 (2H, d, *J* = 7.8, H Ar); 7.28–7.19 (2H, m, H Ar); 7.07 (1H, t, *J* = 7.4, H Ar); 6.96 (1H, d, *J* = 7.4, H Ar); 6.74 (1H, t, *J* = 7.4, H Ar); 6.60 (1H, d, *J* = 7.4, H Ar); 5.24 (1H, s, CH); 4.28 (1H, d, *J* = 16.0, CH_2); 4.25 (1H, br. s, NH); 4.06 (1H, d, *J* = 16.0, CH_2); 2.38 (3H, s, CH_3); 2.20 (1H, br. s, NH). ^{13}C NMR spectrum (50 MHz), δ, ppm: 144.3; 139.4; 138.5; 129.8; 127.7; 126.9; 126.6; 121.9; 118.5; 115.7; 69.9; 46.9; 21.5.

2-(4-Methoxyphenyl)-1,2,3,4-tetrahydroquinazoline (3f).[7] Yield 63 mg (55%), pale-yellow crystals, mp 104–106°C (mp 105–107°C[7]) ^{1}H NMR spectrum (200 MHz), δ, ppm (*J*, Hz): 7.46 (2H, d, *J* = 8.5, H Ar); 7.11–7.02 (1H, m, H Ar); 6.98–6.92 (3H, m, H Ar); 6.74 (1H, t, *J* = 7.3, H Ar); 6.59 (1H, d, *J* = 7.9, H Ar); 5.21 (1H, s, CH), 4.29 (1H, d, *J* = 16.6, CH_2); 4.15 (1H, br. s, NH); 4.00 (1H, d, *J* = 16.6, CH_2); 3.84 (3H, s, OCH_3); 3.83 (1H, br. s, NH). ^{13}C NMR spectrum (101 MHz), δ, ppm: 159.2; 143.3; 133.3; 127.2; 126.7; 125.7; 120.7; 117.6; 114.5; 113.5; 68.6; 54.8; 46.0.

2-(4-Nitrophenyl)-1,2,3,4-tetrahydroquinazoline (3g).[7] Yield 101 mg (82%), white crystals, mp 102–105°C (mp 105–107°C[7]) ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 8.27 (2H, d, *J* = 8.5, H Ar); 7.76 (2H, d, *J* = 8.5, H Ar); 7.12 (1H, t, *J* = 7.9, H Ar); 6.97 (1H, d, *J* = 7.5, H Ar); 6.79 (1H, t, *J* = 7.4, H Ar); 6.68 (1H, d, *J* = 8.0, H Ar); 5.41 (1H, s, CH); 4.21 (1H, d, *J* = 16.6, CH_2), 4.20 (1H, br. s, NH), 3.93 (1H, d, *J* = 16.7, CH_2); 2.0 (1H, br. s, NH). ^{13}C NMR spectrum (101 MHz), δ, ppm: 149.1; 148.3; 145.1; 128.3; 127.9; 126.7; 124.3; 121.8; 119.2; 115.8; 68.8; 45.8.

2-Methyl-2-phenyl-1,2,3,4-tetrahydroquinazoline (3h).[7] The pure compound was not isolated, compound signals indicated from the spectra of the crude. ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 7.52–7.48 (5H, m, H Ar); 7.34 (1H, t, *J* = 7.1, H Ar); 7.14–7.06 (1H, m, H Ar); 6.74–6.65 (2H, m, H Ar); 3.79 (1H, d, *J* = 16.8, CH_2); 3.57 (1H, d, *J* = 16.8, CH_2); 1.65 (3H, s, CH_3); 2NH signals were not detected. ^{13}C NMR spectrum (50 MHz), δ, ppm: 145.6; 142.3; 128.4; 127.3; 127.2; 126.5; 126.1; 120.8; 117.3; 114.3; 69.7; 43.0; 32.4.

2,2-Dimethyl-1,2,3,4-tetrahydroquinazoline (3i).[7] Colorless oil. The pure compound was not isolated, compound signals indicated from the spectra of the crude. ^{1}H NMR spectrum (200 MHz), δ, ppm (*J*, Hz): 7.15 (1H, dd, *J* = 8.0, *J* = 7.4, H Ar); 6.95 (1H, d, *J* = 7.4, H Ar); 6.70 (1H, t, *J* = 7.4, H Ar); 6.49 (1H, d, *J* = 8.0, H Ar); 4.02 (2H, s, CH_2); 1.40 (6H, s, CH_3); 2NH signals were not detected. ^{13}C NMR spectrum (50 MHz), δ, ppm: 142.7; 127.2; 126.1; 119.9; 117.4; 115.0; 64.5; 42.6; 28.4.

The University of Perugia for the financial support "Fondo Ricerca di Base 2017" is warmly acknowledged.

F.M. acknowledges National Consortium of the Italian University C.I.N.M.P.I.S. for the fellowship.

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