

[Hmim]TFA catalyzed multicomponent reaction: direct, mild, and efficient procedure for the synthesis of 1,2-dihydroquinazoline derivatives

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Abstract 4-Substituted-spiro-1,2-dihydroquinazolines and related compounds were synthesized by direct reaction of 2-aminobenzophenones, isatin, or 1,2-diketone derivatives and ammonium acetate in the presence of dual role catalyst-solvent ionic liquid, [Hmim]TFA. Excellent conversion of starting materials was achieved to the desired 1,2-dihydroquinazoline products.

Keywords Multicomponent reaction · 1,2-Dihydroquinazolines · Ionic liquid

Introduction

A multicomponent reaction is one of the most efficient synthetic methods for organic molecules and has proven to be very important for drug discovery [1–4]. The 1,2-dihydroquinazoline compound family has a rich pharmacology with reported nitric oxide synthase (NOS) inhibitors and anti-inflammatory efficiency (Fig. 1) [5,6].

A few examples of the 1,2-dihydroquinazoline ring-system have been reported in the literature. The reaction of 2-aminobenzamidine with benzaldehyde [7] or acetone [8] and microwave irradiation of 2-(aminoaryl)alkanone *O*-phenyl oximes with carbonyl compounds [9] are two synthetic approaches for generation of 1,2-dihydroquinazolines.

Isatin(2,3-dioxindole) and its derivatives have interesting biological properties and are widely used as precursors for many natural products [10]. *N*-alkyl isatin derivatives also were represented in the area of medicinal chemistry and screened against Gram-positive and Gram-negative bacteria [11]. Therefore, herein we disclose a synthetic route that allows access to high yields of a variety of 4-substituted-spiro-1,2-dihydroquinazolines and related compounds.

Recently, ionic liquids (ILs) have become the focus of research in the search for “green” alternatives of traditional organic solvents due to their ability to dissolve a variety of organic, inorganic, and metal complex materials, to activate different reactions and non-volatile nature, and to their potential for recycling [12,13]. In view of the emerging importance of imidazolium-based ILs [14,15] as novel reaction media, we also explored the use of 1-methylimidazolium trifluoroacetate, [Hmim]TFA, as a promoter solvent and acidic catalyst for preparation of 1,2-dihydroquinazoline derivatives under relatively mild conditions.

Experimental

Melting points were measured with an electrothermal 9200 apparatus and were not corrected. Mass spectra were recorded on a Finnigan-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Bomem MB-Series FT-IR spectrophotometer. ¹H and ¹³C NMR spectra were recorded on a Bruker DRX-300 Avance spectrometer at 300.13 and 75.47 MHz, respectively. In all cases, NMR spectra were obtained in solution of DMSO-*d*₆ using TMS as internal standard. The NMR signals also are reported in ppm. Elemental analysis was performed with an VarioEL apparatus in CHNS mode. All the products are new compounds, which were characterized by IR, ¹H NMR and

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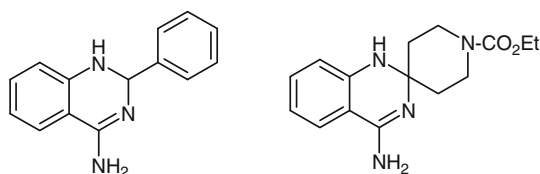


Fig. 1 Bioactive 1,2-dihydroquinazoline cores

^{13}C NMR spectra, and mass spectroscopy as well as CHN analysis.

To a magnetically stirred mixture of 2-aminobenzophenone derivative **1** (1.0 mmol), isatin or 1,2-dicarbonyl derivative **2** (1.0 mmol), and ammonium acetate (0.07 g, 1.0 mmol), 1-methylimidazolium trifluoroacetate ([Hmim]TFA) (0.02 g, 0.1 mmol) was added at 80 °C. After reaction completion (monitored by TLC, ethyl acetate/*n*-hexane 1:3), water was added, the precipitate separated by filtration and then recrystallized from EtOH to afford pure desired products **3a–n**.

6'-Chloro-4'-phenyl-1'*H*-spiro[indoline-3,2'-quinazolin]-2-one (3a)

Yellow solid; mp 274–276 °C; yield: 287 mg (80%).

IR (KBr): 3280, 1732, 1612, 1467, 742 cm^{-1} .

^1H NMR (300.13 MHz, $\text{DMSO}-d_6$) : δ = 6.65 (s, 1H, NH), 6.87–7.48 (m, 12H, H_{arom}), 10.36 (s, 1H, NHCO).

^{13}C NMR (75.47 MHz, $\text{DMSO}-d_6$) δ = 76.08 (C_{spiro}), 110.58, 116.04, 116.22, 120.26, 122.83, 124.98, 127.26, 128.51, 128.83, 128.89, 129.35, 130.24, 130.60, 133.25, 133.70, 137.22, 141.16, 145.49 (C_{arom}), 147.52 ($\text{C}=\text{N}$), 176.01 ($\text{C}=\text{O}$).

MS (EI, 70 eV): m/z (%) = 359 (M^+ , 20), 331 (100), 296 (20), 77 (23), 51 (20).

Anal. Calcd for $\text{C}_{21}\text{H}_{14}\text{ClN}_3\text{O}$: C, 70.10; H, 3.92; N, 11.68. Found: C, 69.95; H, 4.07; N, 11.83.

6'-Chloro-1-methyl-4'-phenyl-1'*H*-spiro[indoline-3,2'-quinazolin]-2-one (3b)

Yellow solid; mp 223–225 °C; yield: 268 mg (72%).

IR (KBr): 3314, 1706, 1615, 1460, 745 cm^{-1} .

^1H NMR (300.13 MHz, $\text{DMSO}-d_6$) δ = 3.15 (s, 3H, CH_3 -N), 6.66 (s, 1H, NH), 6.69–7.51 (m, 12H, H_{arom}).

^{13}C NMR (75.47 MHz, $\text{DMSO}-d_6$) δ = 26.47 (CH_3 -N), 75.83 (C_{spiro}), 109.49, 116.12, 116.22, 120.41, 123.48, 124.62, 127.35, 128.82, 128.94, 130.27, 130.74, 133.03, 133.31, 137.19, 142.72, 145.44 (C_{arom}), 165.59 ($\text{C}=\text{N}$), 174.26 ($\text{C}=\text{O}$).

MS (EI, 70 eV): m/z (%) = 373 (M^+ , 75), 344 (90), 281 (23), 77 (100), 51 (80).

Anal. Calcd for $\text{C}_{22}\text{H}_{16}\text{ClN}_3\text{O}$: C, 70.68; H, 4.31; N, 11.24. Found: C, 70.55; H, 4.43; N, 11.36.

1-Benzyl-6'-chloro-4'-phenyl-1'*H*-spiro[indoline-3,2'-quinazolin]-2-one (3c)

Yellow solid; mp 220–222 °C; yield: 337 mg (75%).

IR (KBr): 3317, 1706, 1610, 1464, 759 cm^{-1} .

^1H NMR (300.13 MHz, $\text{DMSO}-d_6$) δ = 4.90 (s, 2H, CH_2), 6.95 (s, 1H, NH), 7.29–7.56 (m, 17H, H_{arom}).

^{13}C NMR (75.47 MHz, $\text{DMSO}-d_6$) δ = 43.04 (CH_2 -Ph), 75.96 (C_{spiro}), 110.12, 116.14, 120.44, 123.57, 124.86, 127.39, 127.76, 127.96, 128.85, 128.98, 129.13, 130.31, 130.59, 133.13, 133.38, 136.39, 137.17, 141.74, 145.48 (C_{arom}), 165.68 ($\text{C}=\text{N}$), 174.47 ($\text{C}=\text{O}$).

MS (EI, 70 eV): m/z (%) = 450 (M^+ , 40), 420 (100), 358 (40), 281 (23), 91 (100).

Anal. Calcd for $\text{C}_{28}\text{H}_{20}\text{ClN}_3\text{O}$: C, 74.74; H, 4.48; N, 9.34. Found: C, 74.57; H, 4.65; N, 9.51.

5-Bromo-6'-chloro-4'-phenyl-1'*H*-spiro[indoline-3,2'-quinazolin]-2-one (3d)

Yellow solid; mp 298–300 °C; yield: 307 mg (70%).

IR (KBr): 3076, 1706, 1608, 1556, 1283, 701 cm^{-1} .

^1H NMR (300.13 MHz, $\text{DMSO}-d_6$) δ = 6.76 (s, 1H, NH), 6.80–8.44 (m, 11H, H_{arom}), 10.42 (s, 1H, NHCO).

^{13}C NMR (75.47 MHz, $\text{DMSO}-d_6$) δ = 76.38 (C_{spiro}), 112.46, 114.19, 114.32, 115.04, 117.43, 127.62, 128.31, 128.37, 128.46, 128.58, 129.28, 130.06, 133.18, 133.72, 136.33, 137.76, 140.62, 146.28 (C_{arom}), 166.53 ($\text{C}=\text{N}$), 174.54 ($\text{C}=\text{O}$).

MS (EI, 70 eV): m/z (%) = 439 (M^+ , 30), 378 (60), 105 (45), 77 (100), 51 (60).

Anal. Calcd for $\text{C}_{21}\text{H}_{13}\text{BrClN}_3\text{O}$: C, 57.49; H, 2.99; N, 9.58. Found: C, 57.38; H, 3.11; N, 9.70.

6'-Chloro-5-fluoro-4'-phenyl-1'*H*-spiro[indoline-3,2'-quinazolin]-2-one (3e)

Yellow solid; mp 152–155 °C; yield: 327 mg (87%).

IR (KBr): 3284, 1726, 1614, 1480, 790 cm^{-1} .

^1H NMR (300.13 MHz, $\text{DMSO}-d_6$) δ = 4.37 (s, 1H, NH), 6.67–7.45 (m, 11H, H_{arom}), 10.37 (s, 1H, NHCO).

^{13}C NMR (75.47 MHz, $\text{DMSO}-d_6$) δ = 76.42 (C_{spiro}), 111.50, 112.80, 116.01, 116.19, 116.82, 120.44, 127.39, 128.78, 128.95, 130.25, 133.31, 135.26, 135.35, 137.18, 137.58, 145.32, 157.15, 160.31 (C_{arom}), 165.65 ($\text{C}=\text{N}$), 175.93 ($\text{C}=\text{O}$).

MS (EI, 70 eV): m/z (%) = 379 (M^{+2} , 20), 377 (M^+ , 60), 349 (100), 136 (20), 77 (20), 51 (20).

Anal. Calcd for $\text{C}_{21}\text{H}_{13}\text{ClFN}_3\text{O}$: C, 66.76; H, 3.47; N, 11.12. Found: C, 66.57; H, 3.65; N, 11.31.

6'-Chloro-5-nitro-4'-phenyl-1'*H*-spiro[indoline-3,2'-quinazolin]-2-one (**3f**)

Yellow solid; mp 236–238 °C; yield: 331 mg (82%).

IR (KBr): 3412 (NH), 2892, 1675, 1614, 1455, 1337, 1260, 722 cm⁻¹.

¹H NMR (300.13 MHz, DMSO-*d*₆) δ = 6.99 (s, 1H, NH), 7.10–9.06 (m, 11H, H_{arom}), 11.29 (s, 1H, NHCO).

¹³C NMR (75.47 MHz, DMSO-*d*₆) δ = 86.53 (C_{spiro}), 115.42, 116.35, 123.18, 124.66, 127.55, 127.72, 128.48, 128.54, 128.83, 129.34, 129.98, 130.88, 133.08, 135.89, 142.80, 143.18, 144.11, 147.98 (C_{arom}), 148.13 (C=N), 167.35 (C=O).

MS (EI, 70 eV): m/z (%) = 404 (M⁺, 50), 402 (100), 376 (95), 321 (50), 177 (45), 77 (85), 51 (70).

Anal. Calcd for C₂₁H₁₃ClN₄O₃: C, 62.31; H, 3.24; N, 13.84. Found: C, 62.11; H, 3.43; N, 14.04.

6'-Chloro-4'-phenyl-1'*H*,2*H*-spiro[acenaphthylene-1,2'-quinazolin]-2-one (**3g**)

Red solid; mp 207–210 °C; yield: 307 mg (78%).

IR (KBr): 3371, 1713, 1608, 1464, 777 cm⁻¹.

¹H NMR (300.13 MHz, DMSO-*d*₆) δ = 5.65 (s, 1H, NH), 6.64–8.35 (m, 12H, H_{arom}).

¹³C NMR (75.47 MHz, DMSO-*d*₆) δ = 79.45 (C_{spiro}), 115.93, 116.35, 120.43, 121.53, 123.69, 126.33, 127.46, 128.83, 128.96, 129.25, 129.70, 129.89, 130.26, 130.42, 132.81, 133.51, 137.22, 140.59, 141.18, 145.62 (C_{arom}), 165.03 (C=N), 199.76 (C=O).

MS (EI, 70 eV): m/z (%) = 394 (M⁺, 30), 365 (100), 289 (70), 165 (50), 77 (23), 51 (25).

Anal. Calcd for C₂₅H₁₅ClN₂O: C, 76.05; H, 3.83; N, 7.09. Found: C, 75.91; H, 3.97; N, 7.23.

(6-Chloro-2,4-diphenyl-1,2-dihydroquinazolin-2-yl)-phenylmethanone (**3h**)

Orange solid; mp 158–160 °C; yield: 359 mg (85%).

IR (KBr): 3436, 1750, 1683, 1450, 1531, 1379, 694 cm⁻¹.

¹H NMR (300.13 MHz, DMSO-*d*₆) δ = 6.86 (s, 1H, NH), 7.08–8.55 (m, 18H, H_{arom}).

¹³C NMR (75.47 MHz, DMSO-*d*₆) δ = 81.73 (C_{quaternary}), 116.19, 117.34, 120.40, 126.86, 127.32, 128.62, 128.74, 128.87, 129.00, 129.21, 129.71, 130.45, 131.14, 133.31, 133.47, 133.62, 137.48, 141.68, 146.48, 164.69 (C_{arom}), 167.79 (C=N), 197.09 (C=O).

MS (EI, 70 eV): m/z (%) = 423 (M⁺, 30), 393 (50), 315 (75), 281 (75), 77 (100), 51 (80).

Anal. Calcd for C₂₇H₁₉ClN₂O: C, 76.68; H, 4.53; N, 6.62. Found: C, 76.52; H, 4.68; N, 6.77.

4'-Phenyl-1'*H*-spiro[indoline-3,2'-quinazolin]-2-one (**3i**)

Light yellow solid; mp 142–145 °C; yield: 260 mg (80%).

IR (KBr): 3280, 1732, 1612, 1467, 742 cm⁻¹.

¹H NMR (300.13 MHz, DMSO-*d*₆) δ = 6.58 (s, 1H, NH), 6.71–7.86 (m, 13H, H_{arom}), 10.35 (s, 1H, NHCO).

¹³C NMR (75.47 MHz, DMSO-*d*₆) δ = 76.08 (C_{spiro}), 110.58, 116.04, 116.22, 120.26, 122.83, 124.98, 127.26, 128.51, 128.83, 128.89, 129.35, 130.24, 130.60, 133.25, 133.70, 137.22, 141.16, 145.49 (C_{arom}), 147.52 (C=N), 176.01 (C=O).

MS (EI, 70 eV): m/z (%) = 325 (M⁺, 50), 249 (100), 234 (45), 77 (50), 51 (45).

Anal. Calcd for C₂₁H₁₅N₃O: C, 77.52; H, 4.65; N, 12.91. Found: C, 77.40; H, 4.78; N, 13.05.

1-Methyl-4'-phenyl-1'*H*-spiro[indoline-3,2'-quinazolin]-2-one (**3j**)

Yellow solid; mp 232–235 °C; yield: 254 mg (75%).

IR (KBr): 3324, 1706, 1610, 1458, 765 cm⁻¹.

¹H NMR (300.13 MHz, DMSO-*d*₆) δ = 3.13 (s, 3H, CH₃-N), 6.61 (s, 1H, NH), 6.63–7.42 (m, 13H, H_{arom}).

¹³C NMR (75.47 MHz, DMSO-*d*₆) δ = 26.43 (CH₃-N), 75.80 (C_{spiro}), 109.39, 114.36, 115.15, 117.37, 123.39, 124.39, 128.29, 128.62, 129.04, 129.98, 130.57, 133.32, 133.65, 137.81, 142.57, 146.46 (C_{arom}), 166.52 (C=N), 174.68 (C=O).

MS (EI, 70 eV): m/z (%) = 339 (M⁺, 25), 310 (100), 234 (20), 180 (30), 77 (45), 51 (20).

Anal. Calcd for C₂₂H₁₇N₃O: C, 77.86; H, 5.05; N, 12.38. Found: C, 77.70; H, 5.21; N, 12.54.

1-Benzyl-4'-phenyl-1'*H*-spiro[indoline-3,2'-quinazolin]-2-one (**3k**)

Yellow solid; mp 200–202 °C; yield: 323 mg (78%).

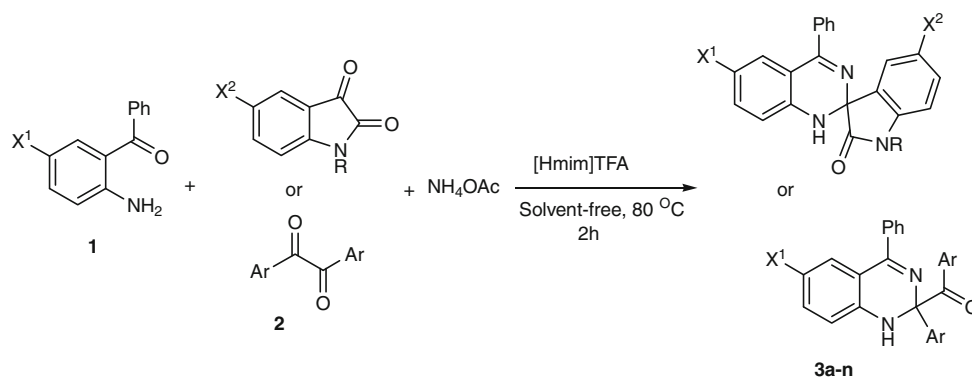
IR (KBr): 3365, 1705, 1610, 1469, 747 cm⁻¹.

¹H NMR (300.13 MHz, DMSO-*d*₆) δ = 4.89 (s, 2H, CH₂), 6.62 (s, 1H, NH), 6.68–7.47 (m, 18H, H_{arom}).

¹³C NMR (75.47 MHz, DMSO-*d*₆) δ = 43.03 (CH₂-Ph), 75.95 (C_{spiro}), 110.02, 114.39, 115.12, 117.42, 123.51, 124.63, 127.71, 127.97, 128.35, 128.66, 129.06, 129.13, 130.04, 130.43, 133.43, 133.73, 136.39, 137.79, 141.58, 146.48 (C_{arom}), 166.64 (C=N), 174.88 (C=O).

MS (EI, 70 eV): m/z (%) = 416 (M⁺, 30), 415 (M⁺, 25), 387 (80), 324 (70), 281 (70), 91 (100).

Anal. Calcd for C₂₈H₂₁N₃O: C, 80.94; H, 5.09; N, 10.11. Found: C, 80.78; H, 5.23; N, 10.24.



Scheme 1 Synthesis of 1,2-dihydroquinazoline derivatives

5-Bromo-4'-phenyl-1'*H*-spiro[indoline-3,2'-quinazolin]-2-one (3l)

Yellow solid; mp 240–242 °C; yield: 294 mg (73%).

IR (KBr): 3436, 1683, 1531, 1379, 694 cm⁻¹.

¹H NMR (300.13 MHz, DMSO-*d*₆) δ = 6.62 (s, 1H, NH), 6.63–7.44 (m, 12H, H_{arom}), 10.45 (s, 1H, NHCO).

¹³C NMR (75 MHz, DMSO-*d*₆) δ = 76.18 (C_{spiro}), 112.57, 114.09, 114.23, 115.04, 117.40, 127.65, 128.35, 128.37, 128.46, 128.60, 129.08, 130.00, 133.08, 133.70, 136.33, 137.76, 140.62, 146.28 (C_{arom}), 166.58 (C=N), 175.83 (C=O).

MS (EI, 70 eV): *m/z* (%) = 404 (M⁺, 25), 402 (30), 375 (100), 295 (45), 267 (50), 165 (40), 77 (50), 51 (45).

Anal. Calcd for C₂₁H₁₄BrN₃O: C, 62.39; H, 3.49; N, 10.39. Found: C, 62.18; H, 3.67; N, 10.60.

5-Nitro-4'-phenyl-1'*H*-spiro[indoline-3,2'-quinazolin]-2-one (3m)

Yellow solid; mp 234–235 °C; yield: 318 mg (86%).

IR (KBr): 3415, 2849, 1675, 1614, 1451, 1327, 1259, 752 cm⁻¹.

¹H NMR (300.13 MHz, DMSO-*d*₆) δ = 6.82 (s, 1H, NH), 7.02–9.04 (m, 12H, H_{arom}), 10.39 (s, 1H, NHCO).

¹³C NMR (75.47 MHz, DMSO-*d*₆) δ = 86.95 (C_{spiro}), 116.32, 124.59, 124.65, 127.27, 128.13, 128.27, 128.31, 128.35, 128.39, 128.43, 128.51, 128.58, 129.13, 129.18, 129.21, 130.05, 133.85, 143.25 (C_{arom}), 145.22 (C=N), 167.56 (C=O).

MS (EI, 70 eV): *m/z* (%) = 370 (M⁺, 20), 368 (100), 342 (90), 152 (30), 77 (70), 51 (60).

Anal. Calcd for C₂₁H₁₄N₄O₃: C, 68.10; H, 3.81; N, 15.13. Found: C, 67.92; H, 3.98; N, 15.30.

4'-Phenyl-1'*H*,2*H*-spiro[acenaphthylene-1,2'-quinazolin]-2-one (3n)

Yellow solid; mp 202–204 °C; yield: 259 mg (72%).

IR (KBr): 3371, 1715, 1608, 1464, 767 cm⁻¹.

¹H NMR (300.13 MHz, DMSO-*d*₆) δ = 6.80 (s, 1H, NH), 6.82–8.46 (m, 15H, H_{arom}).

¹³C NMR (75.47 MHz, DMSO-*d*₆) δ = 75.78 (C_{spiro}), 112.47, 113.87, 115.38, 119.19, 121.51, 123.21, 124.81, 127.38, 127.87, 129.14, 129.85, 130.15, 130.24, 130.47, 131.51, 131.94, 133.12, 133.36, 136.57, 139.23, 141.33 (C_{arom}), 148.52 (C=N), 170.66 (C=O).

MS (EI, 70 eV): *m/z* (%) = 360 (M⁺, 45), 331 (100), 255 (75), 165 (30), 77 (25), 51 (25).

Anal. Calcd for C₂₅H₁₆N₂O: C, 83.31; H, 4.47; N, 7.77. Found: C, 83.19; H, 4.58; N, 7.89.

Results and discussion

In connection with our research on the use of [Hmim]TFA for the synthesis of heterocyclic compounds [16, 17], we would like to disclose here our preliminary results employing mild Brønsted acid as a catalyst (Scheme 1; Table 1). To evaluate the ability of [Hmim]TFA as catalyst in the present study, 1,2-dihydroquinazolines (3a–n) were synthesized by condensation of the keto group of isatin derivatives or 1,2-dicarbonyles (2) with 2-aminobenzophenones (1) and ammonium acetate in the presence of 1-methylimidazolium trifluoroacetate ([Hmim]TFA).

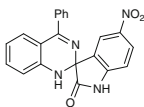
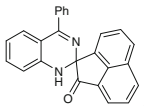
To establish the optimal conditions, initially, we carried out a set of experiments varying the reaction time and amount of the catalyst. The best condition to prepare the 1,2-dihydroquinazolines was achieved using 10 mol% of [Hmim]TFA and 1 equivalent of each reactant at 80 °C for 2 h affording the desired products in good yield.

In order to assess the scope of this procedure, a variety of ketones (aliphatic and aromatic) and 1,2-diketones were condensed with 2-aminobenzophenones and NH₄OAc under similar reaction conditions. We found that while the reaction failed with ketones, when using 1 equivalent of 1,2-diketones instead of isatin the reaction proceeded smoothly at 80 °C affording the corresponding 1,2-dihydroquinazolines 3g, 3h, and 3n in high yields (Scheme 1; Table 1).

Table 1 One-pot three-component synthesis of 1,2-dihydroquinazoline derivatives **3a–n**

Entry	2-Aminobenzophenone 1	2	Product 3	Mp (°C)	Yield (%) ^a
1				274–276	80
2	1a			223–225	72
3	1a			220–222	75
4	1a			298–300	70
5	1a			152–155	87
6	1a			236–238	82
7	1a			207–210	78
8	1a			158–160	85
9		2a		142–145	80
10	1b	2b		232–235	75
11	1b	2c		200–202	78
12	1b	2d		240–242	73

Table 1 continued

Entry	2-Aminobenzophenone 1	2	Product 3	Mp (°C)	Yield (%) ^a
13	1b	2f	 3m	234–235	86
14	1b	2g	 3n	202–204	72

^a Isolated pure product based on 2-aminobenzophenone **1**

In the ¹H NMR spectra desired products exhibited distinct singlets between δ 4.36 and 6.96 that are associated to the NH group of the dihydroquinazoline ring. In the ¹³C NMR spectra, the sp³-hybridized quaternary carbon atoms are identified at low field between δ 75.78 and 81.73. Mass spectrum analysis confirmed molecular weight of the expected products.

Conclusion

In summary, we have developed a simple and efficient method to prepare 4-substituted-spiro-1,2-dihydroquinazolines and related compounds with high yield in the presence of [Hmim]TFA that has both solvent and catalyst character. The synthesis of these compounds is now more convenient, clean, and efficient. There is no need to use polar aprotic solvents such as DMF or any other solvents in general resulting in a minimum generation of waste and cost associated to their disposal.

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