Tetrahedron Letters 49 (2008) 7171–7173

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

An easy and versatile synthesis of ureas from 2-benzylaminopyrimidine

Michiel Van Gool [a,*], José M. Bartolomé [a], Gregor J. Macdonald [b,*]

[a] Johnson & Johnson Pharmaceutical Research and Development, Division of Janssen-Cilag, Neuroscience Medicinal Chemistry Department, Jarama 75, 45007 Toledo, Spain
[b] Johnson & Johnson Pharmaceutical Research and Development, Division of Janssen Pharmaceutica N.V., Neuroscience Medicinal Chemistry Department, Turnhoutseweg 30, B2340 Beerse, Belgium

ARTICLE INFO

Article history:
Received 21 July 2008
Revised 26 September 2008
Accepted 30 September 2008
Available online 2 October 2008

Keywords:
Synthesis
Ureas
2-Benzylaminopyrimidine
Triphosgene

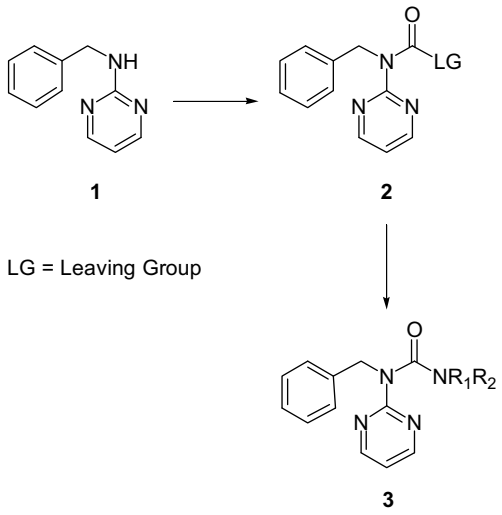
ABSTRACT

A general procedure for the easy and versatile synthesis of ureas from 2-benzylaminopyrimidine is described. This methodology involves the preparation of a highly reactive carbamoyl chloride intermediate that can be further reacted with a high variety of different amines, including highly hindered secondary amines and deactivated anilines with excellent yields. Furthermore, this smooth procedure is compatible with a second functionality on the amine.

As part of one of our Neuroscience Drug Discovery programs, we were interested in the synthesis of a highly diverse set of urea derivatives of 2-alkylamino pyrimidines. For the development of a methodology amenable for the high-throughput parallel synthesis of the desired final compounds, 2-benzylaminopyrimidine **1**[1] was selected as a suitable model system (Scheme 1).

The most classical approach involving the reaction of **1** with isocyanates was rapidly discarded—Firstly, due to the low reactivity of 2-benzylaminopyrimidine **1** under all reaction conditions investigated[2] and secondly, because of the limited diversity of commercially available isocyanates that would limit the diversity of the set of final compounds. Consequently, a different strategy for the preparation of compounds **3** following an indirect approach was considered. This strategy involves the formation of a reactive intermediate **2** that by further reaction with amines would afford the desired urea derivatives **3** (Scheme 1). This two-step methodology offers a number of advantages, such as a larger and more diverse set of commercial building blocks (amines vs isocyanates) and access to tetrasubstituted ureas, not possible via the classical route.

Our first attempt consisted of reacting **1** with 1,1′-carbonyldiimidazole (CDI), followed by addition of the amine, according to a previously described procedure for similar compounds.[3] However, this approach failed and no final compounds were detected in any of the different conditions tried,[4] probably due again to the low reactivity of our aminopyrimidine model hampering the formation of intermediate **2**.

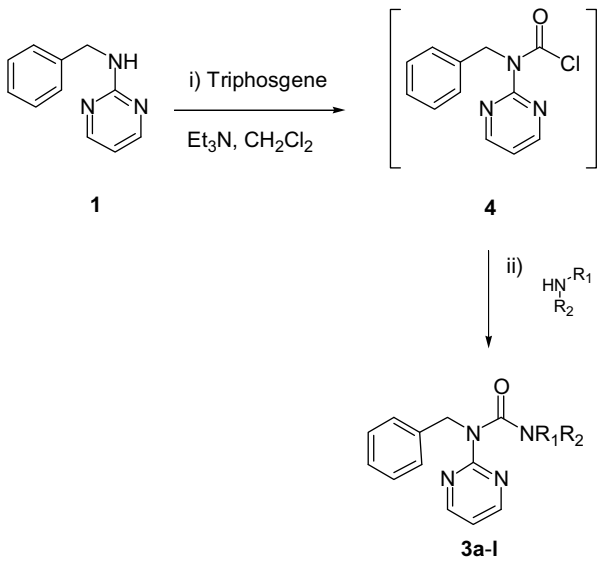


Scheme 1.

Finally, our last attempt targeted the preparation of **2** according to a similar procedure described for the synthesis of [1,2,4]triazolo-[1,5-*a*]pyrimidinium betaines from 2-alkylaminopyrimidines.[5] Thus, reaction of **1** with triphosgene in dichloromethane at room temperature followed by addition of ethylamine furnished desired compound **3a** (Scheme 2, Table 1) in an excellent yield. Furthermore, here it is shown that the intermediate **4** is sufficiently

* Corresponding authors. Tel.: +34 925 245 750; fax: +34 925 245 771 (M.V.G.).
E-mail address: mvgool2@prdes.jnj.com (M. Van Gool).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.09.171



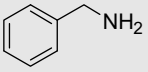
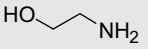
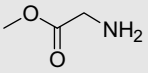
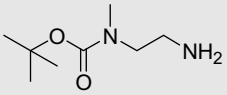
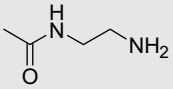
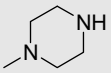
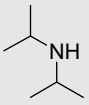
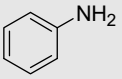
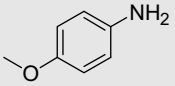
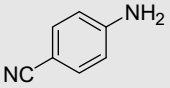
Scheme 2.

activated to react with a high diversity of amines under mild conditions allowing the preparation of the desired urea derivatives **3** with good to excellent overall yields. This procedure has proven to be general enough to allow the easy synthesis of tri- and tetrasubstituted urea derivatives of 2-benzylaminopyrimidine including those compounds from reaction with highly sterically hindered secondary amines and deactivated anilines.

Reaction of 2-benzylaminopyrimidine **1** with a slight excess (0.4 equiv) of triphosgene in the presence of triethylamine[6] (2.4 equiv) in dichloromethane[7] at room temperature afforded after 10 min of incubation, the carbamoyl chloride **4**. The formation of this intermediate was confirmed by LC/MS analysis of the reaction mixture. Thus, a mixture of carbamoyl chloride **4** and its corresponding methyl carbamate (formed by reaction of **4** with the methanol used as eluent) was observed. Subsequent addition of the corresponding amines, either aliphatic or aromatic (1.6 equiv), furnished desired urea derivatives **3a–l** (Table 1).[8] In most of the examples, total conversion to the final product was observed after few minutes of reaction time. Only when either a highly hindered amine (diisopropylamine **3i**) or a deactivated aniline (4-cyanoaniline **3l**) was used, longer reaction times of 7 hours and 1 h, respectively, were required. Final yields after standard work-up and purification ranged from a good 72% to an excellent 92%, and were not affected by the reactivity of the amines used.[9] Furthermore, this mild methodology is compatible with the presence of a second functionality in the amine (**3c–f**) that may be subject for a further derivatization. Noteworthy in the case of 2-aminoethanol, no reaction of the hydroxyl group was observed (**3c**). Additionally, as shown in examples **3g–i**, this procedure allows the straightforward formation of tetrasubstituted ureas.

In conclusion, here we have reported a general procedure that allows the easy and versatile synthesis of ureas from 2-benzylaminopyrimidine. This methodology involves the preparation of a highly reactive carbamoyl chloride intermediate that can be further reacted with a high variety of different amines, including highly hindered secondary amines and deactivated anilines with excellent yields. Furthermore, this smooth procedure is compatible with a second functionality on the amine. Further exploration of this procedure on other low reactive systems is currently in progress, and will be reported in due course.

Table 1
Synthesis of final compounds **3a–l** produced via Scheme 2

Entry	Amine	Reaction time[a]	Isolated yield
3a		10 min	81[b]
3b		10 min	81[b]
3c		10 min	88[b]
3d		10 min	83[b]
3e		10 min	85[b]
3f		10 min	82[b]
3g		20 min	92[b]
3h		20 min	90[b]
3i		7 h	80[b]
3j		10 min	73[c]
3k		10 min	72[c]
3l		1 h	80[d]

[a] Reaction time after addition of the corresponding amine.
[b] Yield after chromatographic purification.
[c] Yield after chromatographic purification and crystallization from acetonitrile.
[d] Yield after chromatographic purification and crystallization from methanol.

Acknowledgments

The highly valuable collaboration and help of Mr. Alberto Fontana with the generation of the reported analytical data is gratefully acknowledged.

References and notes

1. Cherng, Y. J. *Tetrahedron* **2002**, *58*, 887–890.
2. Reaction of **1** with ethyl and phenyl isocyanate (1 or 5 equiv of isocyanate) was tested using dichloromethane, tetrahydrofuran and toluene as solvents at temperatures ranging from room temperature to 110 °C. Addition of a base to the reaction media (diisopropylethylamine) was also investigated. Under all the reactions conditions tried no satisfactory amounts of desired products **3a** or **3j** respectively were obtained.
3. Keizer, H. M.; Sijbesma, R. P.; Meijer, E. W. *Eur. J. Org. Chem.* **2004**, *12*, 2553–2555.
4. Compound **1** was reacted with CDI at temperatures ranging from room temperature to 65 °C followed by addition of ethylamine and aniline and further reaction at temperatures ranging between room temperature and 50 °C in either chloroform or tetrahydrofuran as solvents.
5. Marley, H.; Wright, S. H. B. J.; Preston, P. *Chem. Soc., Perkin Trans. I* **1989**, *10*, 1727–1733.

6. When diisopropylethylamine was added similar results were obtained but no reaction at all was observed when an inorganic base (K_2CO_3) was used.
7. Tetrahydrofuran and acetonitrile were also investigated as solvents, furnishing similar results.
8. *General procedure*: To a solution of **1** (100 mg, 0.54 mmol) and triethylamine (0.18 ml, 1.30 mmol) in CH_2Cl_2 (3 ml) a solution of triphosgene (64 mg, 0.216 mmol) in CH_2Cl_2 (1 ml) was added. The reaction mixture was stirred at room temperature for 10 min and then the corresponding amines (0.864 mmol) were added. After completion of the reaction (reaction times are shown in Table 1), the corresponding mixtures were diluted with CH_2Cl_2 (25 ml) and washed with 10% NH_4Cl aqueous solution. The organic layers were separated, dried (Na_2SO_4), filtered and evaporated under vacuum. The residues thus obtained were purified by Flash silica gel column chromatography (eluent CH_2Cl_2/MeOH gradient from 100/0 to 98/2). The desired fractions were collected and evaporated yielding the urea derivatives **3a**–**l**. Compounds **3j**–**l** were further crystallized from CH_3CN (**3j**,**k**) or MeOH (**3l**).
9. Analytical data: Melting points were determined in open capillary tubes on a Mettler FP62 apparatus and are uncorrected. NMR spectra were recorded on a Bruker DPX-400 with standard pulse sequences operating at 400 MHz for ^1H NMR and at 101 MHz for ^{13}C NMR. Chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane (TMS). High-resolution mass spectra were recorded on a Micromass LCT Time of Flight mass spectrometer configured with an electrospray ionization source, maintained at 140 °C, using nitrogen as the nebulizer gas and Lockmass device for mass calibration using Leucine-Enkephaline as standard substance. Spectra were acquired in positive ionization mode by scanning from 100 to 750 in 0.5 s using a dwel time of 0.1 s. The capillary needle voltage was 2.5 kV and the cone voltage was 20 V. Data acquisition was performed with MassLynk-Openlynx software. Compound **3a**: white solid; mp 78.9 °C; ^1H NMR ($CDCl_3$) δ 1.25 (t, J = 7.26 Hz, 3H) 3.38–3.50 (m, 2H) 5.47 (s, 2H) 6.82 (t, J = 4.77 Hz, 1H) 7.12–7.21 (m, 1H) 7.25 (t, J = 7.46 Hz, 2H) 7.38 (d, J = 7.67 Hz, 2H) 8.47 (d, J = 4.77 Hz, 2H) 10.13 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 15.39 (CH_3) 35.77 (CH_2) 47.14 (CH_2) 113.91 (CH) 126.69 (CH) 127.78 (CH) 128.24 (CH) 139.61 (C) 156.02 (C) 157.18 (CH) 160.08 (C); ESI-HRMS m/z calcd for $C_{14}H_{17}N_4O$ $[MH]^+$ 257.1402. Found: 257.1413. *Compound* **3b**: white solid; mp 78.8 °C; ^1H NMR ($CDCl_3$) δ 4.64 (d, J = 5.60 Hz, 2H) 5.50 (s, 2H) 6.81 (t, J = 4.87 Hz, 1H) 7.14–7.21 (m, 1H) 7.22–7.29 (m, 3H) 7.29–7.43 (m, 6H) 8.45 (d, J = 4.77 Hz, 2H) 10.53–10.71 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 44.94 (CH_2) 47.33 (CH_2) 114.09 (CH) 126.79 (CH) 127.26 (CH) 127.57 (CH) 127.81 (CH) 128.31 (CH) 128.75 (CH) 139.47 (2 × C) 156.34 (C) 157.27 (CH) 160.03 (C); ESI-HRMS m/z calcd for $C_{19}H_{19}N_4O$ $[MH]^+$ 319.1559. Found: 319.1571. *Compound* **3c**: syrup; ^1H NMR ($CDCl_3$) δ 3.45 (br s, 1H) 3.56 (q, J = 5.04 Hz, 2H) 3.78 (t, J = 4.98 Hz, 2H) 5.46 (s, 2H) 6.83 (t, J = 4.87 Hz, 1H) 7.17 (s, 1H) 7.25 (t, J = 7.57 Hz, 2H) 7.35 (d, J = 7.46 Hz, 2H) 8.48 (d, J = 4.77 Hz, 2H) 10.47–10.56 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 43.80 (CH_2) 47.33 (CH_2) 63.13 (CH_2) 114.30 (CH) 126.82 (CH) 127.67 (CH) 128.31 (CH) 139.25 (C) 157.32 (CH) 157.56 (C) 159.86 (C); ESI-HRMS m/z calcd for $C_{14}H_{17}N_4O_2$ $[MH]^+$ 273.1352. Found: 273.1358. *Compound* **3d**: white solid; mp 76.7 °C; ^1H NMR ($CDCl_3$) δ 3.76 (s, 3H) 4.21 (d, J = 5.39 Hz, 2H) 5.47 (s, 2H) 6.85 (t, J = 4.87 Hz, 1H) 7.12–7.21 (m, 1H) 7.25 (t, J = 7.46 Hz, 2H) 7.37 (d, J = 7.46 Hz, 2H) 8.51 (d, J = 4.77 Hz, 2H) 10.72 (t, J = 4.66 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 42.98 (CH_2) 47.32 (CH_2) 52.36 (CH_3) 114.38 (CH) 126.81 (CH) 127.68 (CH) 128.30 (CH) 139.19 (C) 156.31 (C) 157.33 (CH) 159.84 (C) 171.19 (C); ESI-HRMS m/z calcd for $C_{15}H_{17}N_4O_3$ $[MH]^+$ 301.1301. Found: 301.1321. *Compound* **3e**: syrup; ^1H NMR ($CDCl_3$) δ 1.41 (s, 9H) 2.85–2.98 (m, 3H) 3.42–3.51 (m, 2H) 3.51–3.60 (m, 2H) 5.47 (s, 2H) 6.84 (t, J = 4.77 Hz, 1H) 7.17 (s, 1H) 7.25 (t, J = 7.46 Hz, 2H) 7.36 (d, J = 7.46 Hz, 2H) 8.49 (d, J = 4.98 Hz, 2H) 10.35 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 28.55 (CH_3) 34.88 (CH_3) 38.78 (C) 39.27 (C) 47.15 (CH_2) 47.91 (C) 48.73 (C) 114.09 (CH) 126.73 (CH) 127.64 (CH) 128.27 (CH) 139.40 (C) 156.33 (C) 157.26 (CH) 159.94 (C); ESI-HRMS m/z calcd for $C_{20}H_{28}N_5O_3$ $[MH]^+$ 386.2192. Found: 386.2171. *Compound* **3f**: white solid; mp 208.6 °C; ^1H NMR ($CDCl_3$) δ 1.89 (s, 3H) 3.40–3.49 (m, 2H) 3.55 (q, J = 5.87 Hz, 2H) 5.47 (s, 2H) 6.75 (br s, 1H) 6.88 (t, J = 4.87 Hz, 1H) 7.18 (s, 1H) 7.25 (t, J = 7.36 Hz, 2H) 7.34 (d, J = 7.05 Hz, 2H) 8.51 (d, J = 4.77 Hz, 2H) 10.48 (t, J = 5.39 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 23.32 (CH_3) 40.03 (CH_2) 41.37 (CH_2) 47.29 (CH_2) 114.42 (CH) 126.84 (CH) 127.48 (CH) 128.33 (CH) 139.19 (C) 157.33 (CH) 157.55 (C) 159.80 (C) 170.88 (C); ESI-HRMS m/z calcd for $C_{16}H_{20}N_5O_2$ $[MH]^+$ 314.1617. Found: 314.1627. *Compound* **3g**: white solid; mp 107.4 °C; ^1H NMR ($CDCl_3$) δ 3.38 (m, 8H) 5.10 (s, 2H) 6.73 (t, J = 4.87 Hz, 1H) 7.20–7.35 (m, 3H) 7.43 (d, J = 7.26 Hz, 2H) 8.42 (d, J = 4.77 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 45.38 (CH_2) 50.21 (CH_2) 66.46 (CH_2) 113.30 (CH) 127.67 (CH) 128.60 (CH) 128.98 (CH) 137.97 (C) 157.20 (C) 158.31 (CH) 160.69 (C); ESI-HRMS m/z calcd for $C_{16}H_{19}N_4O_2$ $[MH]^+$ 299.1508. Found: 299.1517. *Compound* **3h**: white solid; mp 86.4 °C; ^1H NMR ($CDCl_3$) δ 2.12 (br s, 4H) 2.18 (s, 3H) 3.40 (br s, 4H) 5.09 (s, 2H) 6.72 (t, J = 4.77 Hz, 1H) 7.21–7.27 (m, 1H) 7.31 (t, J = 7.26 Hz, 2H) 7.43 (d, J = 7.05 Hz, 2H) 8.41 (d, J = 4.77 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 44.89 (CH_2) 46.09 (CH_3) 50.22 (CH_2) 54.55 (CH_2) 113.17 (CH) 127.53 (CH) 128.54 (C) 128.97 (CH) 138.10 (C) 157.14 (C) 158.26 (CH) 160.79 (C); ESI-HRMS m/z calcd for $C_{17}H_{22}N_5O$ $[MH]^+$ 312.1824. Found: 312.1836. *Compound* **3i**: syrup; ^1H NMR ($CDCl_3$) δ 0.93–1.20 (m, 12H) 3.41–3.75 (m, 2H) 4.94–5.17 (m, 2H) 6.67 (t, J = 4.77 Hz, 1H) 7.20–7.36 (m, 3H) 7.45 (d, J = 7.05 Hz, 2H) 8.38 (d, J = 4.77 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 20.13 (CH + CH_3) 49.95 (CH_2) 112.65 (CH) 127.57 (CH) 128.52 (CH) 129.70 (CH) 138.04 (C) 156.31 (C) 158.12 (CH) 161.33 (C); ESI-HRMS m/z calcd for $C_{18}H_{25}N_4O$ $[MH]^+$ 313.2028. Found: 313.2046. *Compound* **3j**: white solid; mp 162.1 °C; ^1H NMR ($CDCl_3$) δ 5.55 (s, 2H) 6.88 (t, J = 4.87 Hz, 1H) 7.07 (t, J = 7.46 Hz, 1H) 7.15–7.22 (m, 1H) 7.22–7.29 (m, 2H) 7.32 (t, J = 7.88 Hz, 2H) 7.42 (d, J = 7.46 Hz, 2H) 7.61 (d, J = 7.46 Hz, 2H) 8.54 (d, J = 4.77 Hz, 2H) 12.63 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 47.13 (CH_2) 114.42 (CH) 120.62 (CH) 123.71 (CH) 126.92 (CH) 127.87 (CH) 128.36 (CH) 129.10 (CH) 138.98 (C) 139.13 (C) 153.49 (C) 157.34 (CH) 159.76 (C); ESI-HRMS m/z calcd for $C_{18}H_{17}N_4O$ $[MH]^+$ 305.1402. Found: 305.1397. *Compound* **3k**: white solid; mp 151.8 °C; ^1H NMR ($CDCl_3$) δ 3.78 (s, 3H) 5.54 (s, 2H) 6.82–6.91 (m, 3H) 7.15–7.21 (m, 1H) 7.26 (t, J = 7.46 Hz, 2H) 7.42 (d, J = 7.46 Hz, 2H) 7.50 (d, J = 8.71 Hz, 2H) 8.53 (d, J = 4.98 Hz, 2H) 12.42 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 47.11 (CH_2) 55.68 (CH_3) 114.28 (2 × CH) 122.41 (CH) 126.88 (CH) 127.90 (CH) 128.33 (CH) 132.05 (C) 139.22 (C) 153.73 (C) 156.14 (C) 157.30 (CH) 159.78 (C); ESI-HRMS m/z calcd for $C_{19}H_{19}N_4O_2$ $[MH]^+$ 335.1508. Found: 335.1497. *Compound* **3l**: white solid; mp 196.2 °C; ^1H NMR ($CDCl_3$) δ 5.55 (s, 2H) 7.00 (t, J = 4.87 Hz, 1H) 7.17–7.25 (m, 1H) 7.24–7.32 (m, 2H) 7.41 (d, J = 7.26 Hz, 2H) 7.60 (d, J = 8.71 Hz, 2H) 7.74 (d, J = 8.71 Hz, 2H) 8.61 (d, J = 4.77 Hz, 2H) 13.07 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 47.24 (CH_2) 106.26 (C) 114.87 (CH) 119.36 (C) 120.18 (CH) 127.12 (CH) 127.82 (CH) 128.43 (CH) 133.34 (CH) 138.58 (C) 143.23 (C) 153.14 (C) 157.46 (CH) 159.52 (C); ESI-HRMS m/z calcd for $C_{19}H_{16}N_5O$ $[MH]^+$ 330.1355. Found: 330.1368.