Thiourea as a Precursor to Sophisticated Heterobicyclic Compounds by a Double Annulation Reaction

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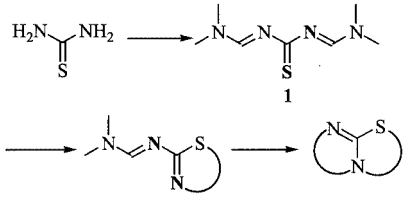
We report here the first example of an efficient regioselective synthesis of heterobicyclic compounds using thiourea as starting material. The key step in this synthetic process is the preparation of *N*,*N*′-bis[(dimethylamino)methylene]thiourea (**1**), which reacts as thiazadiene, leading to diazadiene heterocycles. These heterocycles give either thiazolopyrimidine **4** or imidazo-1,3-thiazine **7** by a double annulation reaction.

Introduction

Over the past few years heterobicyclic compounds have been extensively investigated with regard to their numerous applications in pharmaceutical and agrochemical research. Considerable efforts have been undertaken to exploit synthetic routes to these compounds.[1−3] Among those, imidazo-1,3-thiazines represent a rare class of heterocyclic rings, whereas thiazolopyrimidine derivatives have been broadly examined. For example, Ritanserin finds applications in several psychopharmacological fields,[4,5] while benzothiazolopyrimidine derivatives have been evaluated for their affinity at the central benzodiazepine receptor.[6] On the other hand, some thiazolo[3,2-*a*]pyrimidines have recently been reported to be active against HIV-1 as annulated analogues of HEPT,[7] while other series of these compounds have been successfully tested as anti-inflammatory agents by Tozkoparan and co-workers.[8,9] Therefore, we were prompted to devise a novel and widely applicable method which provides control of the regioselectivity of these heterocyclic rings. In the course of our ongoing research, we recently reported an annulation protocol towards heterobicyclic compounds using an aminothiazole[10,11] or aminothiazine[12] as the starting monocycle. These considerations, as well as our strong background in heterocyclic chemistry,[13−16] led us to develop a new polyheteropolyenic precursor to build these systems. We have chosen to prepare *N*,*N*′-bis[(dimethylamino)methylene]thiourea (**1**), which can react at first as a thiazadiene for the first cyclisation, and then as a diazadiene to give the heterobicyclic compounds (Scheme 1). We present here a new and efficient three-step method for the synthesis of complex heterobicyclic compounds using thiourea as starting material.



Scheme 1

Results and Discussion

With the aim of investigating the reactivity of the synthon **1** we first performed an alkylation reaction and then a [4 + 2] cycloaddition reaction. We also performed the same syntheses but in reverse order. In this manner, we obtained two radically different heterobicyclic compounds, a thiazolopyrimidine and an imidazo-1,3-thiazine, from the same starting materials (Scheme 2).

One of the most powerful methods for producing skeleton **1** is through the condensation of dimethylformamide dimethylacetal (DMF-DMA) on thiourea in boiling dichloromethane. Liebscher has reported the synthesis and use of such synthons, but his work was restricted to the preparation of monocycles.[17] The reaction between polyheteropolyene **1** and *p*-bromophenacyl bromide afforded, as the sole product, the corresponding *S*-alkyl bromide salt, due to the nucleophilicity of the sulfur atom (Scheme 3).

This intermediate, which was not isolated, was deprotonated in situ by addition of triethylamine. Annulation

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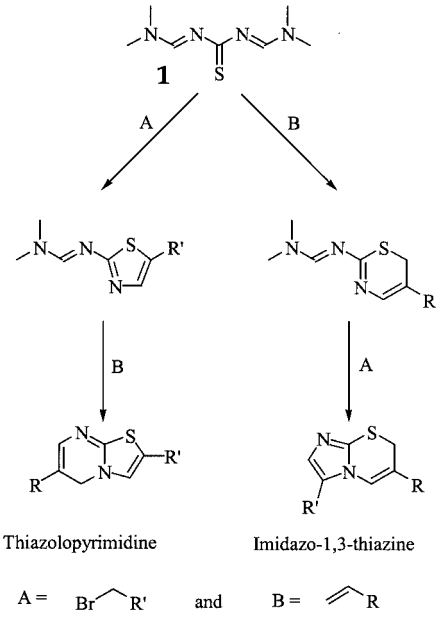
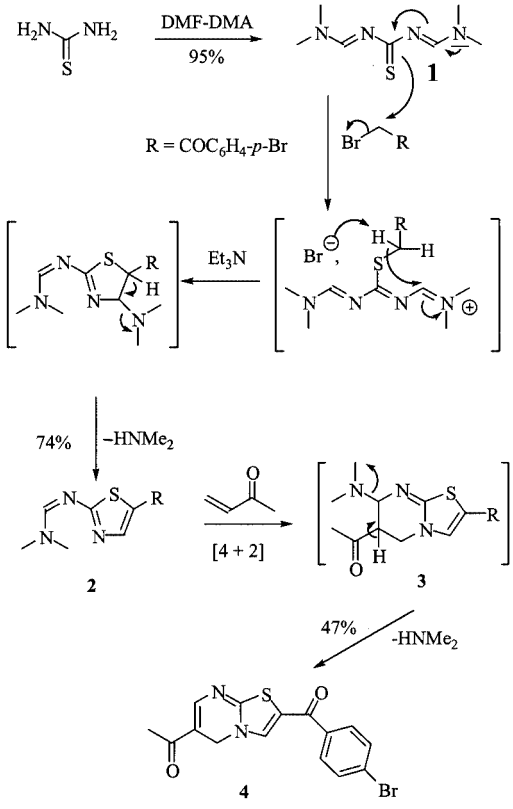


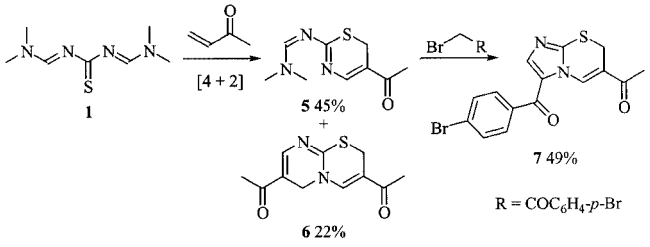
Scheme 2



Scheme 3

proceeded spontaneously followed by loss of dimethylamine to provide *N*′-[5-(*p*-bromobenzoyl)thiazol-2-yl]-*N*,*N*-dimethylimidoformamide (**2**) in good yield. The [4 + 2] cycloaddition reaction between thiazole **2**, bearing a diazadienic chain, and methyl vinyl ketone as an acrylic dienophile, gave rise to 5*H*-thiazolo[3,2-*a*]pyrimidine **4** in modest yield. In this reaction, the intermediate **3** was never isolated and the final step consisted of deamination of the supposed cycloadduct giving the fused heterocycle **4**.

By a similar synthetic strategy, when the polyheteropolyenic precursor **1** reacted with methyl vinyl ketone, the thiazole **5** was formed (Scheme 4). This [4 + 2] cycloaddition reaction occurs in a regiocontrolled manner and proceeded as expected, followed once again by spontaneous deamination to afford compound **5** in 45% yield. The modest yield is due to a double condensation of the dienophile before complete consumption of the starting material giving 2*H*,6*H*-pyrimido[2,1-*b*][1,3]thiazine **6**.



Scheme 4

Upon reaction with α-bromo ketone, the alkylation of compound **5** affected the endocyclic nitrogen atom providing the *N*-alkylated unisolated salt. Subsequent treatment with triethylamine afforded the cycloadduct, leading to the desired compound after deamination. The most successful conditions found were to perform the alkylation in boiling tetrahydrofuran for 24 h and then to use 2 equiv. of base, yielding imidazo[2,1-*b*][1,3]thiazine **7** in 49% yield. All compounds showed the expected spectroscopic properties and satisfactory elemental analyses and mass spectra were obtained.

Conclusion

In summary, *N*,*N*′-bis[(dimethylamino)methylene]thiourea (**1**) has been used as a versatile building block for the synthesis of a wide range of heterocyclic motifs, including imidazo-1,3-thiazine and thiazolopyrimidine. The chemistry described in this report provides a concise and facile route for rather complicated fused heterocyclic scaffolds with a high selectivity. We are currently investigating the scope of these reactions by extending them to other acyl bromides and dienophiles. The results of these studies will be reported in due course.

Experimental Section

General Remarks: All reagents were purchased from Acros Organics or Aldrich. All chemicals were reagent grade and used without further purification; all solvents were freshly distilled before use. The CNRS Analysis Laboratory (Vernaison) performed the

elemental analyses. Column chromatography was conducted on silica gel 60 (40−63 μm), available from E. Merck. Melting points measured using a Reichert microscope are uncorrected. The ^1H and ^{13}C NMR spectra were recorded at room temperature using a Bruker AC200 operating at 50 and 200 MHz, respectively. Chemical shifts (δ) are given in ppm downfield from tetramethylsilane as internal standard. Mass spectra were determined with a Hewlett Packard 5989 spectrometer. The ir spectra were obtained using a Bruker Vector 22 spectrometer.

***N*,*N*′-Bis[(dimethylamino)methylene]thiourea (1):** A suspension of thiourea (10 mmol) and *N*,*N*-dimethylformamide dimethylacetal (30 mmol) in dichloromethane (10 mL) was refluxed for 4 h. After removal of the solvent, compound **1** was recrystallised from diethyl ether to afford a yellow amorphous solid (1.77 g, 95%), m.p. 139 °C. IR (KBr): $\tilde{\nu}$ = 2920, 2360, 1646, 1606, 1416, 1333, 1258, 1228, 1102, 975 cm^{-1}. ^1H NMR (200 MHz, [D$_6$]DMSO, 25 °C): δ = 3.00, 3.15 [2 s, 12 H, 2 N(C*H*$_3$)$_2$], 8.68 (2 s, 2 H, C*H*N) ppm. ^{13}C NMR (50 MHz, [D$_6$]DMSO, 25 °C): δ = 35.4, 40.9 [4 C, N(*C*H$_3$)$_2$], 161.3 (2 C, *C*HN), 207.6 (*C*S) ppm. MS (CI): *m*/*z* (%) = 115 (20) [M$^+$ − NCHN(CH$_3$)$_2$], 99 (24), 71 (39). $C_7H_{14}N_4S$ (186.3): calcd. C 45.14, H 7.58, N 30.08; found C 45.38, H 7.87, N 29.89.

***N*′-[5-(*p*-Bromobenzoyl)thiazol-2-yl]-*N*,*N*-dimethylformamide (2):** A solution of *p*-bromophenacyl bromide (5 mmol) and thiourea **1** (5 mmol) in dichloromethane (10 mL) was stirred under nitrogen at room temperature for 15 min and then NEt_3 (10 mmol) was added. The reaction mixture was then stirred for a further 20 h at room temperature. After removal of the solvent, the residue was chromatographed with dichloromethane/ethyl acetate (4:1) as eluent. Compound **2** was recrystallised from diethyl ether as a yellow solid (1.25 g, 74%), m.p. 163 °C. IR (KBr): $\tilde{\nu}$ = 2917, 1626, 1608, 1453, 1393 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 3.15, 3.18 [2 s, 6 H, 2 N(C*H*$_3$)$_2$], 7.65−7.69 (m, 4 H, C*H*$_{ar}$), 7.81 (s, 1 H, 4-*H*), 8.36 (s, 1 H, NC*H*) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 35.3, 41.2 [2 C, N(*C*H$_3$)$_2$], 126.8 (S*C*CO), 130.3, 131.7 (4 *C*H$_{ar}$), 132.0, 137.2 (2 *C*$_{ar}$), 149.2 (*C*-4), 156.5 (N*C*H), 181.2 (S*C*N), 186.0 (*C*O) ppm. MS (CI): *m*/*z* (%) = 339/337 (63/60) [M$^+$], 306/304 (19/19) [M$^+$ − SH], 155 (32), 154 (100) [M$^+$ − BrC$_6$H$_4$CO], 98 (28). $C_{13}H_{12}BrN_3OS$ (338.2): calcd. C 46.17, H 3.58, N 12.42; found C 46.42, H 3.83, N 12.57.

Thiazolo[3,2-*a*]pyrimidine 4: A mixture of an amidine **2** (4 mmol) and methyl vinyl ketone (5 mL) was stirred at reflux for 4 d. The resulting solution was concentrated under reduced pressure and the residue was purified by chromatography on silica, with dichloromethane as eluent, to yield **4** (0.68 g, 47%) as a yellow crystals, m.p. 234 °C. IR (KBr): $\tilde{\nu}$ = 1618, 1589, 1493, 1410, 1327, 1249, 1180 cm^{-1}. ^1H NMR (200 MHz, CF_3CO_2D, 25 °C): δ = 2.57 (s, 3 H, COC*H*$_3$), 5.29 (s, 2 H, C*H*$_2$), 7.79 (s, 1 H, NC*H*), 7.82 (s, 4 H, C*H*$_{ar}$), 8.11 (s, 1 H, NC*H*) ppm. ^{13}C NMR (50 MHz, CF_3CO_2D, 25 °C): δ = 25.1 (CO*C*H$_3$), 48.8 (*C*H$_2$), 115.3 (*C*CO), 132.2, 135.2 (4 *C*H$_{ar}$), 133.5, 133.8, 134.8, 136.0, 138.6 (2 *C*$_{ar}$, 2 *C*H, S*C*CO), 165.6 (S*C*N), 188.3, 201.7 (2 *C*O) ppm. MS (CI): *m*/*z* (%) = 364/362 (100/97) [M$^+$], 349/347 (16/16), 321/319 (13/13), 282 (9), 185/183 (25/23), 157/155 (17/17). $C_{15}H_{11}BrN_2O_2S$ (363.2): calcd. C 49.60, H 3.05, N 7.71; found C 49.85, H 3.21, N 7.49.

***N*′-(5-Acetyl-6*H*-1,3-thiazin-2-yl)-*N*,*N*-dimethylimidoformamide (5):** Methyl vinyl ketone (20 mmol) was added to a solution of thiourea **1** (4 mmol) in dichloromethane (10 mL). The reaction mixture was stirred for 18 h at room temperature and then diluted with acetone (80 mL). The solution was filtered through a short pad of Celite and concentrated under reduced pressure. Purification by flash column chromatography (silica gel; ethyl acetate/acetone, 3:2) afforded compound **5** as a yellow liquid (0.38 g, 45%). IR (film): $\tilde{\nu}$ = 1642, 1625, 1377, 1468, 1296, 1236, 1206, 1120 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 2.37 (s, 3 H, COC*H*$_3$), 3.15, 3.18 [2 s, 6 H, 2 N(C*H*$_3$)$_2$], 3.67 (s, 2 H, SC*H*$_2$), 7.81 (s, 1 H, 4-*H*), 8.36 (s, 1 H, NC*H*) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 22.9 (S*C*H$_2$), 25.0 (CO*C*H$_3$), 35.6, 41.4 [2 C, N(*C*H$_3$)$_2$], 114.1 (*C*CO), 150.1 (*C*-4), 157.3 (N*C*H), 169.4 (S*C*N), 195.9 (*C*O) ppm. MS (CI): *m*/*z* (%) = 212 (62) [M + H$^+$], 144 (74), 104 (91), 88 (100). $C_9H_{13}N_3OS$ (211.3): calcd. C 51.16, H 6.20, N 19.89; found C 51.02, H 6.11, N 19.97.

Pyrimido[2,1-*b*][1,3]thiazine 6: Yield: 22% (0.21 g), yellow crystals, m.p. 236 °C. IR (KBr): $\tilde{\nu}$ = 1664, 1648, 1502, 1397, 1244, 1148 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 2.31, 2.35 (2 s, 6 H, COC*H*$_3$), 3.71 (d, *J* = 0.9 Hz, 2 H, SC*H*$_2$), 4.49 (d, *J* = 1.2 Hz, 2 H, NC*H*$_2$), 6.99 (t, *J* = 0.9 Hz, 1 H, 4-*H*), 7.36 (t, *J* = 1.2 Hz, 1 H, 8-*H*) ppm. ^{13}C NMR (50 MHz, [D$_6$]DMSO, 25 °C): δ = 21.2 (S*C*H$_2$), 24.7, 25.0 (2 CO*C*H$_3$), 47.4 (N*C*H$_2$), 117.0, 117.2 (2 *C*CO), 143.6, 144.7 (*C*-4, *C*-8), 159.4 (S*C*N), 193.9, 194.8 (2 *C*O) ppm. MS (CI): *m*/*z* (%) = 236 (63) [M + H$^+$], 219 (5), 193 (15), 151 (13), 43 (100). $C_{11}H_{12}N_2O_2S$ (236.3): calcd. C 55.92, H 5.12, N 11.86; found C 56.06, H 4.98, N 11.82.

Imidazo[2,1-*b*][1,3]thiazine 7: A solution of *p*-bromophenacyl bromide (1.1 mmol) and formamide **5** (1 mmol) in THF (10 mL) was refluxed for 6 h. After cooling to room temperature, NEt_3 (2.2 mmol) was added. The reaction mixture was further stirred at room temperature for 24 h, diluted with CH_2Cl_2 (100 mL) and washed with H_2O (100 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 70 mL). The combined organic layers were washed with H_2O (3 × 70 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by flash chromatography with dichloromethane/ethyl acetate (9:1) to furnish compound **7**, which was recrystallised from diethyl ether as a white solid (0.18 g, 49%), m.p. 203 °C. IR (KBr): $\tilde{\nu}$ = 1671, 1638, 1579, 1417, 1368, 1165, 1003 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 2.50 (s, 3 H, COC*H*$_3$), 3.91 (d, *J* = 0.9 Hz, 2 H, SC*H*$_2$), 7.63 (s, 1 H, NC*H*), 7.64−7.75 (m, 4 H, C*H*$_{ar}$), 8.66 (t, *J* = 0.9 Hz, 1 H, NC*H*) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 21.4 (S*C*H$_2$), 25.2 (CO*C*H$_3$), 119.6 (*C*CO), 128.0, 129.7, 136.5 (N*C*CO, 2 *C*$_{ar}$), 130.2, 132.0 (4 *C*H$_{ar}$), 134.8, 142.4 (2 *C*H), 150.3 (S*C*N), 182.9, 194.4 (2 *C*O) ppm. MS (CI): *m*/*z* (%) = 364/362 (43/39) [M$^+$], 296/294 (100/91), 185/183 (46/46), 157/155 (39/41). $C_{15}H_{11}BrN_2O_2S$ (363.2): calcd. C 49.60, H 3.05, N 7.71; found C 49.47, H 2.95, N 7.83.

Acknowledgments

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[1] T. L. Gilchrist, *J. Chem. Soc., Perkin Trans. 1* **2001**, *20*, 2491−2515.
[2] I. Collins, *J. Chem. Soc., Perkin Trans. 1* **2000**, *21*, 2845−2861.
[3] S. Jayakumar, M. P. S. Ishar, M. P. Mahajan, *Tetrahedron* **2002**, *58*, 379−471.
[4] F. Claudi, L. Scoccia, G. Giorgioni, G. Marucci, A. Di Stefano, S. Gessi, A. Siniscalchi, P. Andrea Borea, *Eur. J. Med. Chem.* **1998**, *33*, 705−713.
[5] M. Van Laar, E. Volkerts, M. Verbaten, *Psychopharmacology* **2001**, *154*, 189−197.
[6] S. P. Gupta, A. Paleti, *Bioorg. Med. Chem.* **1998**, *6*, 2213−2218.

[7] K. Danel, E. B. Pedersen, C. Nielsen, *J. Med. Chem.* **1998**, *41*, 191−198.
[8] B. Tozkoparan, M. Ertan, B. Krebs, M. Läge, P. Kelicen, R. Demirdamar, *Arch. Pharm. Pharm. Med. Chem.* **1998**, *331*, 201−206.
[9] B. Tozkoparan, M. Ertan, P. Kelicen, R. Demirdamar, *Farmaco* **1999**, *54*, 588−593.
[10] C. Landreau, D. Deniaud, A. Reliquet, J. C. Meslin, *Synthesis* **2001**, *13*, 2015−2020.
[11] C. Landreau, D. Deniaud, M. Evain, A. Reliquet, J. C. Meslin, *J. Chem. Soc., Perkin Trans. 1* **2002**, *6*, 741−745.
[12] C. Landreau, D. Deniaud, A. Reliquet, J. C. Meslin, *Synthesis* **2002**, *3*, 403−408.
[13] C. Friot, A. Reliquet, F. Reliquet, J. C. Meslin, *Synthesis* **2000**, *5*, 695−702.
[14] C. Landreau, D. Deniaud, F. Reliquet, A. Reliquet, J. C. Meslin, *Heterocycles* **2000**, *53*, 2667−2677.
[15] C. Landreau, D. Deniaud, A. Reliquet, F. Reliquet, J. C. Meslin, *J. Heterocycl. Chem.* **2001**, *38*, 93−98.
[16] J. D. Charrier, C. Landreau, D. Deniaud, A. Reliquet, F. Reliquet, J. C. Meslin, *Tetrahedron* **2001**, *57*, 4195−4202 and references therein.
[17] A. Knoll, J. Liebscher, R. Radeglia, *J. Prakt. Chem.* **1985**, *327*, 463−470.

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