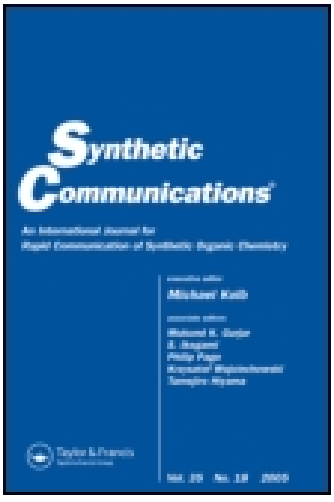

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Efficient Synthesis of 2-Aminothiazole-4-phenyl-5-acetamides via the Open Chain Tautomers of γ-Keto Amides

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Efficient Synthesis of 2-Aminothiazole-4-phenyl-5-acetamides via the Open Chain Tautomers of γ-Keto Amides

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Abstract: A simple and efficient method is described for the synthesis of new functionalized 2-aminothiazoles, the 2-aminothiazole-4-phenyl-5-acetamides 5, in 67–96% yields based on an application of the Hantzsch synthesis. The method involves the reaction of thiourea with 3-benzoyl-3-bromo-propionamides **4** prepared from the corresponding 3-benzoylpropionamides **3**. The tautomeric structure of the γ-keto amides **3** and **6** is directly related to the present study, because 2-aminothiazoles **5** are readily obtained from the corresponding open chain γ-keto amides **3**.

Keywords: 2-Aminothiazole-4-phenyl-5-acetamides, 3-benzoylpropion-amides, 3-benzoyl-3-bromopropionamides

The 2-aminothiazole ring system is a useful structural element in medicinal chemistry and has found broad application in drug development for the treatment, among other diseases, of allergies[1] and bacterial[2] and HIV infections.[3] Given this proven utility, it seems reasonable that the development of libraries of 2-aminothiazoles might provide additional lead molecules for use in drug discovery.

2-Aminothiazoles are prepared by the condensation of α-halo ketones with an appropriate thiourea, a specific case of the well-established and extremely versatile Hantzsch syntesis of the C–C + S–C–N route.[4,5]

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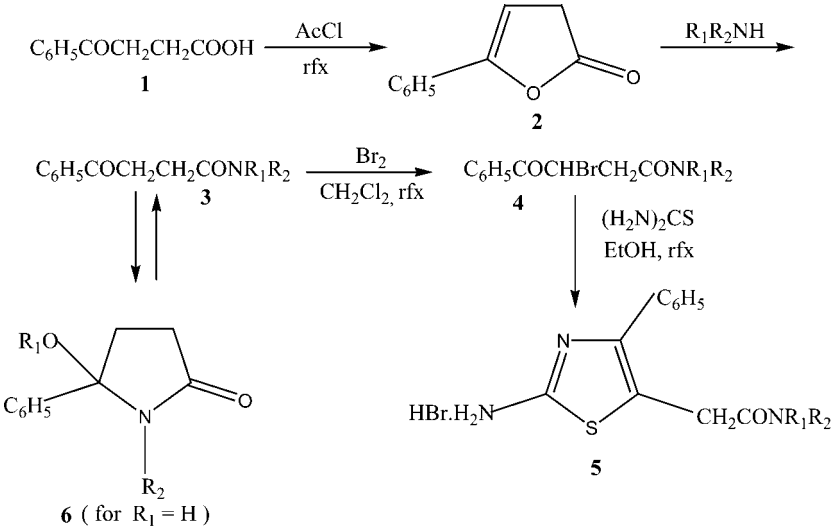
Many preparations of 2-aminothiazoles by conventional procedures have been reviewed[6–8] and tabulated recently.

Herein we report a facile synthesis of the titled compounds. Our synthesis of 2-aminothiazole-4-phenyl-5-acetamides **5** entails the use of the readily prepared 3-benzoyl-3-bromopropionamides **4** (Scheme 1). Treatment of **4** with thiourea in refluxing ethanol for 1 h cleanly afforded 2-aminothiazole-4-phenyl-5-acetamides **5**, which were isolated, as their hydrobromides, in 67–96% yields. However, it was first necessary to synthesize 3-benzoylpropionamides **3**; thus we applied a described method[9,10] for the synthesis of γ-keto amides **3a** and **3b** from 3-benzoylpropionic acid 1 with the reaction sequence that appears in Scheme 1, with a modification[11] in the preparation of 5-phenylfuran-2(3H)-one **2**.

γ-Keto amides of the general formula **3** (R_1=H) are known to exhibit the ring-chain tautomerism[9,10,12a–d] (Scheme 1). The tautomeric structure of the γ-keto amides **3a–3d** has been studied spectroscopically (IR, ^{1}H and ^{13}C NMR), and these compounds were assigned the open chain amide structure **3**.

The tautomerism of the γ-keto amides is directly related to the present study, because the synthesis of the titled compounds **5** are readily obtained from the corresponding open chain γ-keto amides **3**, as described in following sections.

In conclusion, we have prepared a new series of functionalized 2-aminothiazoles in good yields and with high degrees of purity from thiourea and 3-benzoyl-3-bromopropionamides, with an application of the well-known Hantzsch synthesis. The key to this method is the preparation



a: R_1=H, R_2=C_6H_5; b: R_1=H, R_2=$CH_2C_6H_5$; c: R_1=R_2=C_6H_5; d: R_1=R_2=$CH_2C_6H_5$

Scheme 1.

of the open chain tautomers 3-benzoylpropionamides and their conversion to the corresponding (open chain) 3-benzoyl-3-bromopropionamides. Given that the 2-aminothiazole ring system is a useful structural element in medicinal chemistry, these new functionalized 2-aminothiazoles could be considered to be of interest as potential drugs.

EXPERIMENTAL

General

NMR spectra were recorded at ambient temperature using a Varian Gemini 2000 300-MHz spectrometer. The data are reported as follows: chemical shift quoted in ppm on the δ scale, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), and coupling constants given in (Hz). Micro analyses were performed by microanalytical laboratory of CNRS (France). Melting points are reported uncorrected. IR spectra were obtained at a Nicolet Magna 560 spectrometer (as nujol mulls).

5-Phenylfuran-2(3H)-one (2) was prepared from β-benzoylpropionic acid and acetyl chloride at reflux conditions.[11]

3-Benzoylpropionamide-N-phenyl (3a)

A mixture of 8 g (49.95 mmol) of 5-phenylfuran-2(3H)-one and 4.9 g (52.45 mmol) of fresh distilled aniline was heated on a steam bath for 3.5 h. The solid product after recrystallization from ethanol gave 10 g (79%) of a solid, mp 148–149°C, lit.[13] 149°C. IR (Nujol mull, cm^{-1}): 3290, 1678, 1658, 1597, and 1529. ^{1}H NMR ($CDCl_3$): 2.77 (t, $J = 6.2$ Hz, 2H, $>NCOCH_2-$), 3.88 (t, $J = 6.2$ Hz, 2H, $-CH_2COPh$), 7.00–8.18 (m, 10H, arom.), 10.10 (br s, 1H, –NHCO–). ^{13}C NMR ($CDCl_3$): 30.30, 33.40, 120.01, 124.27, 127.42, 128.25, 128.68, 129.17, 133.35, 138.28, 172.36, and 199.46.

3-Benzoylpropionamide-N-benzyl (3b)

A mixture of 8.00 g (49.95 mmol) of 5-phenylfuran-2(3H)-one and 5.62 g (52.45 mmol) of benzylamine was heated on a steam bath for 10 min. The solid product after recrystallization from ethanol gave 11.50 g (86%) of a solid, mp 110–112°C, lit.[10] 110–111°C. IR (Nujol mull, cm^{-1}): 3257, 1681, 1634, and 1550. ^{1}H NMR ($CDCl_3$): 2.70 (t, $J = 6.2$ Hz, 2H, $>NCOCH_2-$), 3.45 (t, $J = 6.2$ Hz, 2H, $-CH_2COPh$), 4.53 (d, $J = 6.5$ Hz, 2H, $>NCH_2Ph$), 6.38 (br m, 1H, –NHCO–), 7.35–8.30 (m, 10 H, arom.). ^{13}C NMR ($CDCl_3$): 30.13, 34.03, 43.61, 127.52, 127.88, 128.26, 128.80, 133.45, 136.76, 138.63, 172.32, 199.51.

3-Benzoylpropionamide-N,N-diphenyl (3c)

A mixture of 18.68 g (116.77 mmol) of 5-phenylfuran-2(3H)-one and 20.75 g (122.60 mmol) of diphenylamine was heated on an oil bath at 120°C for 4.5 h. The dark colored retinous product after recrystallization from ethanol gave 25.72 g (67%) of a solid, mp 147–149°C. Anal. calcd. for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25. Found: C, 79.94; H, 5.94; N, 4.11. IR (Nujol mull, cm^{-1}): 1673, 1647, 1593, and 1583. ^1H NMR ($CDCl_3$): 2.69 (t, $J = 6.2$ Hz, 2H, $>NCOCH_2-$), 3.39 (t, $J = 6.2$ Hz, 2H, $-CH_2COPh$), 7.00–8.36 (m, with as at 7.37 ppm, 15 H, arom.). ^{13}C NMR ($CDCl_3$): 30.11, 33.50, 121.31, 124.35, 127,31, 127.49, 128.41, 128.51, 128.71, 128.95, 129.22, 129.31, 133.33, 133.45, 171.73, 199.41.

3-Benzoylpropionamide-N,N-dibenzyl (3d)

A mixture of 8.00 g (49.95 mmol) of 5-phenylfuran-2(3H)-one and 10.35 g (52.44 mmol) of dibenzylamine was heated on a steam bath for 2 h. The solid product after recrystallization from ethanol gave 16 g (90%) of a solid mp 84–86°C. lit.[14] 84–85°C. Anal. calcd. for $C_{24}H_{23}NO_2$: C, 80.64; H, 6.48; N, 3.92. Found: C, 80.48; H, 6.27; N, 3.69. IR (Nujol mull, cm^{-1}): 1687, 1644, 1605, 1594, and 1581. ^1H NMR ($CDCl_3$): 2,80 (t, $J = 6.2$ Hz, 2H, $>NCOCH_2-$), 3.36 (t, $J = 6.2$ Hz, 2H, $-CH_2COPh$), 4.58 (s, 4H, benzylic protons), 7.13–8.36 (m, 15H, arom.). ^{13}C NMR ($CDCl_3$): 27.37, 33.89, 48,47, 50.03, 126.82, 127.61, 127.87, 128.38, 128.47, 128.81, 128.86, 129.23, 136,73, 137.13, 137.57, 172.69, 199.49.

General Procedure for the Preparation of 3-Benzoyl-3-bromopropion-amides (4a–4d)

A solution of bromine 9.6 mmol in 20 ml of dichloromethane was added slowly to a solution of 3-benzoylpropionamide (**3a–3d**) (8 mmol) in 30–80 ml of dichloromethane, depending on the solubility. Then the solution was refluxed with stirring for 5–20 min until the bromine color disappeared. The solution was concentrated under vacuum, at moderate temperature, and the solid or retinous concentrate recrystallized from ethanol to give an analytical sample of the 3-benzoyl-3-bromopropionamide (**4a–4d**).

Data

3-Benzoyl-3-bromopropionamide-N-phenyl (4a): Yield 85%, mp 110–111°C, lit.[15] 106–111°C. Anal. calcd for $C_{16}H_{14}BrNO_2$: C, 57.85; H, 4.25; Br, 24.05; N, 4.22. Found: C, 57.67; H, 4.11; Br, 24.25; N, 3.99.

IR (Nujol mull, cm^{-1}): 3273, 1688, 1680, 1655, 1595, 1587, 1580, and 1528. ^1H NMR ($CDCl_3$): 2.80–3.87 (m, 2H, $-CH_2-$), 5.68 (dd, $J = 7.1$ Hz, 1H, >CH–), 7.03–7.47 (m, 10H, arom.), 7.82–8.13 (br m, 1H, –NHCO–). ^{13}C NMR ($CDCl_3$): 40.41, 40.87, 121.31, 125.35, 127.52, 128.34, 128.74, 129.26, 133.44, 138.72, 169.58, 193.44.

3-Benzoyl-3-bromopropionamide-N-benzyl (4b): Yield 78%, mp 118–119°C. Anal. calcd. for $C_{17}H_{16}BrNO_2$: C, 58.97; H, 4.66; Br, 23.08; N, 4.04. Found: C, 59.12; H, 4.73; Br, 23.11; N, 3.88. IR (Nujol mull, cm^{-1}): 3320, 1690, 1680, 1636, 1596, 1577, and 1549. ^1H NMR ($CDCl_3$): 2.75–3.66 (m, 2H, $-CH_2-$), 5.70 (dd, $J = 7.2$ Hz, 1H, >CH–), 4.43 (d, $J = 6.2$ Hz, 2H, $-CH_2Ph$), 6.29 (br m, 1H, –NHCO–), 7.27–8.25 (m, 10H, arom.). ^{13}C NMR ($CDCl_3$): 40.74, 40.97, 43.85, 127.90, 128.04, 129.02, 129.09, 129.40, 134.10, 134.25, 138.04, 169.48, 193.28.

3-Benzoyl-3-bromopropionamide-N,N-diphenyl (4c): Yield 81%, mp 121–122°C. Anal. calcd. for $C_{22}H_{18}BrNO_2$: C, 64.72; H, 4.44; Br, 19.57; N, 3.43. Found: C, 64.50; H, 4.31; Br, 19.64; N, 3.52. IR (Nujol mull, cm^{-1}): 1680, 1664, 1592, and 1578. ^1H NMR ($CDCl_3$): 2.73–3.46 (m, 2H, $-CH_2-$), 5.65 and 5.80 (dd, $J = 5.2$ Hz, 1H, >CH–), 7.08–8.31 (m, 15H, arom.). ^{13}C NMR ($CDCl_3$): 40.62, 40.90, 124.05, 125.44, 127.61, 127.93, 128.31, 128.62, 128.97, 129.45, 133.12, 136.03, 136.45, 138.41, 169.42, 193.34.

3-Benzoyl-3-bromopropionamide-N,N-dibenzyl (4d): Yield 83%, mp 104–106°C. Anal. calcd. for $C_{24}H_{22}BrNO_2$: C, 66.06; H, 5.08; Br, 18.31; N, 3.21. Found: C, 65.87; H, 4.83; Br, 18.44; N, 3.30. IR (Nujol mull, cm^{-1}): 1693, 1682, 1648, 1594, 1575, and 1550. ^1H NMR ($CDCl_3$): 3.01–4.07 (m, 2H, $-CH_2-$), 4.50 (s, 4H, benzylic protons), 5.75 and 5.90 (dd, $J = 5.2$ Hz, 1H, >CH–), 7.01–8.31 (m, 15H, arom.). ^{13}C NMR ($CDCl_3$): 40.31, 40.87, 49.41, 50.32, 126.74, 127.50, 127.61, 128.04, 128.11, 128.41, 128.45, 129.31, 136.90, 137.61, 138.90, 169.61, 193.72.

General Procedure for the Preparation of 2-Aminothiazole-4-Phenyl-5-Acetamides (5a–5d)

A mixture of the 3-benzoyl-3-bromopropionamide (**4a–4d**) (5 mmol) and thiourea (7 mmol) in 7–15 ml of ethanol was refluxed for 1 h. After cooling the crystalline solid was filtered and recrystallized from ethanol to give an analytical sample.

Data

2-Aminothiazole-4-phenyl-5-acetamide-N-phenyl, hydrobromide (5a): Yield 74%, mp 224–225°C. Anal. calcd. for $C_{17}H_{16}BrN_3OS$: C, 52.31;

H, 4.13; Br, 20.47; N, 10.76. Found: C, 52.13; H, 3.87; Br, 20.51; N, 10.59. IR (Nujol mull, cm^{-1}): 3286, 3163, 3136, 3105, 1642, 1594, 1536, 1487, 1399, and 1071. ^1H NMR ($CDCl_3$/DMSO-d_6): 3.91 (s, 2H, $-CH_2-$), 7.29–7.83 (m, 10H, arom.), 9.00 (br m, 3H, $-N^+H_3$), 10.50 (s, 1H, –NHCO–).

2-Aminothiazole-4-phenyl-5-acetamide-N-benzyl, hydrobromide (5b): Yield 67%, mp 105–106°C. Anal. calcd. for $C_{18}H_{18}BrN_3OS$: C, 53.47; H, 4.49; Br, 19.76; N, 10.39. Found: C, 53.23; H, 4.21; Br, 19.95; N, 10.11. IR (Nujol mull, cm^{-1}): 3365, 3265, 3077, 1642, 1627, 1598, 1585, 1541, 1491, 1415, and 1081. ^1H NMR ($CDCl_3$/DMSO-d_6): 3.71 (s, 2H, $-CH_2-$), 4.38 (d, $J = 6.2$ Hz, 2H, $-CH_2Ph$), 7.20–7.72 (m, 10H, arom.), 8.62 (br m, 1H, –NHCO–), 8.96 (br m, 3H, $-N^+H_3$).

2-Aminothiazole-4-phenyl-5-acetamide-N,N-diphenyl, hydrobromide (5c): Yield 88%, mp 233–234°C. Anal. calcd. for $C_{23}H_{20}BrN_3OS$: C, 59.23; H, 4.32; Br, 17.13; N, 9.01. Found: C, 58.98; H, 4.11; Br, 17.25; N, 8.83. IR (Nujol mull, cm^{-1}): 3272, 3158, 1648, 1631, 1594, 1572, 1491, 1400, and 1074. ^1H NMR ($CDCl_3$/DMSO-d_6): 3.71 (s, 2H, $-CH_2-$), 7.05–7.73 (m, 15H, arom.), 9.13 (br m, 3H, $-N^+H_3$).

2-Aminothiazole-4-phenyl-5-acetamide-N,N-dibenzyl, hydrobromide (5d): Yield 96%, mp 177–178°C. Anal. calcd. for $C_{25}H_{24}BrN_3OS$: C, 60.73; H, 4.89; Br, 16.16; N, 8.50. Found: C, 60.48; H, 4.69; Br, 16.34; N, 8.37. IR (Nujol mull, cm^{-1}): 3340, 3239, 3194, 1642, 1620, 1603, 1578, 1495, 1406, and 1075. ^1H NMR ($CDCl_3$/DMSO-d_6): 3.89 (s, 2H, $-CH_2-$), 4.48 and 4.67 (two s, 4H, benzylic protons), 6.88–7.53 (m, 15H, arom.), 9.14 (br m, 3H, $-N^+H_3$).

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