ISSN 1070-4280, Russian Journal of Organic Chemistry, 2006, Vol. 42, No. 1, pp. 139–141. © Pleiades Publishing, Inc., 2006.
Original Russian Text © M.V. Vovk, P.S. Lebed', 2006, published in Zhurnal Organicheskoi Khimii, 2006, Vol. 42, No. 1, pp. 145–147.

SHORT COMMUNICATIONS

Non-Isocyanate Synthesis of *N*-(1,3-Thiazol-2-yl)ureas

M. V. Vovk, and P. S. Lebed'

Institute of Organic Chemistry, National Academy of Sciences of Ukraine,
ul. Murmanskaya 5, Kiev, 02094 Ukraine
e-mail: mvovk@i.com.ua

Received April 22, 2005

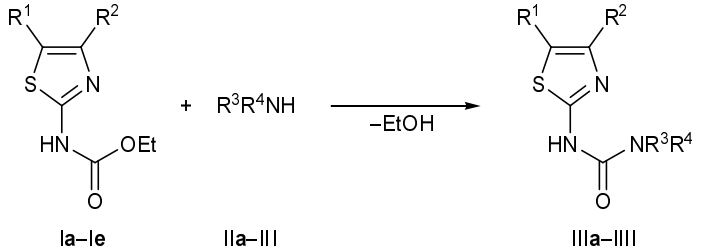
DOI: 10.1134/S1070428006010222

Di- and trisubstituted ureas possessing a thiazole or benzothiazole fragment are known to exhibit pronounced herbicide activity [1–4]. *N*-(2-Thiazolyl)ureas are generally synthesized by reaction of 2-aminothiazoles with isocyanates or carbamoyl chlorides [1–7]. However, some carbamoylating agents of these series are difficultly accessible, and there are certain limitations concerning extension of the above procedure to the synthesis of new thiazolyl-substituted ureas. In the recent time, development of an alternative approach has been initiated. This approach implies preliminary modification of 2-aminothiazoles with chloroformyl derivatives, such as phenyl chloroformate [8], *N*-(chlorocarbonyl)imidazole [9], or *N*-(chlorocarbonyloxy)succinimide [10, 11], followed by reaction of the modified compounds with amines. While developing this approach, we found that *N*-(2-thiazolyl)-ureas can be synthesized using the most accessible 2-aminothiazole derivatives, ethyl 2-thiazolylcarbamates **Ia**–**Ie**. Compounds **Ia**–**Ie** reacted with various aliphatic, aromatic, and heterocyclic amines **IIa**–**IIl** on heating in boiling xylene (mixture of isomers) to give substituted ureas **IIIa**–**IIII** in 76–93% yield.

Ethyl (4-R^1-5-R^2-1,3-thiazol-2-yl)carbamates Ia–Ie (*general procedure*). A mixture of 20 mmol of the corresponding 2-aminothiazole and 2.39 g (22 mmol) of ethyl chloroformate was heated in 25 ml of boiling xylene until it became homogeneous (4–5 h). After cooling, the precipitate was filtered off, washed with hexane, and dried.

Ethyl (1,3-thiazol-2-yl)carbamate (Ia). Yield 77%, mp 151–153°C; published data [12]: mp 150–153°C.

Ethyl [4-(4-methoxyphenyl)-5-methyl-1,3-thiazol-2-yl]carbamate (Ib). Yield 79%, mp 184–186°C. IR spectrum, ν, cm^{-1}: 1725 (C=O), 3210 (N–H). ^{1}H NMR spectrum, δ, ppm: 1.27 t (3H, CH_3), 2.39 s (3H, CH_3), 4.14 q (2H, CH_2), 3.78 s (3H, CH_3), 6.93 d (2H, H_{arom}), 11.22 br.s (1H, NH). Found, %: N 9.39; S 11.21. $C_{14}H_{16}N_2O_3S$. Calculated, %: N 9.58; S 10.97.



Ia–Ie IIa–IIl IIIa–IIII

I, R^1 = R^2 = H (**a**); R^1 = Me, R^2 = 4-MeOC$_6$H$_4$ (**b**); R^1 = MeC(O), R^2 = Me (**c**); R^{1}R^2 = (CH$_2$)$_4$ (**d**); R^{1}R^2 = CH$_2$CH(CH$_3$)(CH$_2$)$_2$ (**e**); **II**, R^3 = H, R^4 = 3-morpholinosulfonylphenyl (**a**), 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydropyrazol-4-yl (**b**), 4-methylpyridin-2-yl (**c**); R^{3}R^{4}N = 3,5-dimethylpiperidino (**d**); R^3 = H, R^4 = 3-CF$_3$C$_6$H$_4$ (**e**); R^{3}R^{4}N = 4-methylpiperazin-1-yl (**f**), R^{3}R^{4}N = 3-ethoxycarbonylpiperidino (**g**); R^3 = H, R^4 = 2-furylmethyl (**h**), 4-CHF$_2$C$_6$H$_4$ (**i**), Ph(CH$_2$)$_3$CH(Me) (**j**), 3-morpholinopropyl (**k**), 3-pyridyl (**l**); **III**, R^1 = R^2 = R^3 = H, R^4 = 3-morpholinosulfonylphenyl (**a**), 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydropyrazol-4-yl (**b**); R^1 = Me, R^2 = 4-MeOC$_6$H$_4$, R^3 = H, R^4 = 4-methylpyridin-2-yl (**c**); R^1 = Me, R^2 = 4-MeOC$_6$H$_4$, R^{3}R^{4}N = 3,5-dimethylpiperidino (**d**); R^1 = MeC(O), R^2 = Me, R^3 = H, R^4 = 3-CF$_3$C$_6$H$_4$ (**e**); R^1 = MeC(O), R^2 = Me, R^{3}R^{4}N = 4-methylpiperazin-1-yl (**f**), 3-ethoxycarbonylpiperidino (**g**); R^{1}R^2 = (CH$_2$)$_4$, R^3 = H, R^4 = 2-furylmethyl (**h**), 4-CHF$_2$C$_6$H$_4$ (**i**); R^{1}R^2 = CH$_2$CH(CH$_3$)(CH$_2$)$_2$, R^3 = H, R^4 = Ph(CH$_2$)$_3$CH(Me) (**j**), 3-morpholinopropyl (**k**), 3-pyridyl (**l**).

Ethyl (5-acetyl-4-methyl-1,3-thiazol-2-yl)carbamate (Ic). Yield 84%, mp 169–170°C. IR spectrum, ν, cm^{-1}: 1680, 1730 (C=O); 3210 (N–H). ^1H NMR spectrum, δ, ppm: 1.30 t (3H, CH_3), 2.43 s (3H, CH_3), 2.53 s (3H, CH_3), 4.22 q (2H, CH_2), 11.98 br.s (1H, NH). Found, %: N 12.45; S 14.12. $C_9H_{12}N_2O_3S$. Calculated, %: N 12.27; S 14.05.

Ethyl (4,5,6,7-tetrahydro-1,3-benzothiazol-2-yl)-carbamate (Id). Yield 78%, mp 188–190°C. IR spectrum, ν, cm^{-1}: 1725 (C=O); 3215 (N–H). ^1H NMR spectrum, δ, ppm: 1.27 t (3H, CH_3), 1.76–1.80 m (4H, CH_2), 2.57–2.62 m (4H, CH_2), 4.18 q (2H, OCH_2), 11.26 br.s (1H, NH). Found, %: N 12.23; S 14.04. $C_{10}H_{14}N_2O_2S$. Calculated, %: N 12.38; S 14.17.

Ethyl (6-methyl-4,5,6,7-tetrahydro-1,3-benzothiazol-2-yl)carbamate (Ie). Yield 83%, mp 193–194°C. IR spectrum, ν, cm^{-1}: 1725 (C=O); 3210 (N–H). ^1H NMR spectrum, δ, ppm: 1.07 d (3H, CH_3), 1.27 t (3H, CH_3), 1.43–2.68 m (7H, CH_2, CH), 4.16 q (2H, OCH_2), 11.29 br.s (1H, NH). Found, %: N 11.83; S 13.50. $C_{11}H_{16}N_2O_2S$. Calculated, %: N 11.66; S 13.34.

***N*-(4-R^1-5-R^2-1,3-Thiazol-2-yl)ureas IIIa–IIIl (*general procedure*).** A mixture of 10 mmol of carbamate **Ia–Ie** and 11 mmol of amine **IIa–III** in 20 ml of xylene was heated for 4 h under reflux. The solvent was distilled off, 15 ml of ethanol was added to the residue, the mixture was heated for 0.5 h under reflux and cooled, and the precipitate was filtered off.

***N*-(3-Morpholinosulfonylphenyl)-*N'*-(1,3-thiazol-2-yl)urea (IIIa).** Yield 90%, mp 219–220°C. IR spectrum, ν, cm^{-1}: 1710 (C=O); 3220–3330 (N–H). ^1H NMR spectrum, δ, ppm: 2.49 s (3H, CH_3), 3.08–3.12 m (4H, NCH_2), 3.60–3.64 m (4H, OCH_2), 7.08 d (1H, thiazole), 7.30 d (2H, H_{arom}), 7.35 d (1H, thiazole), 7.58 d.d (1H, H_{arom}), 7.99 s (1H, H_{arom}), 8.85 s (1H, NH), 10.76 br.s (1H, NH). Found, %: N 15.01; S 17.47. $C_{14}H_{16}N_4O_4S_2$. Calculated, %: N 15.21; S 17.41.

***N*-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-*N'*-(1,3-thiazol-2-yl)urea (IIIb).** Yield 77%, mp 297–300°C. IR spectrum, ν, cm^{-1}: 1680, 1710 (C=O); 3280–3350 (N–H). ^1H NMR spectrum, δ, ppm: 2.23 s (3H, CH_3), 3.08 s (3H, CH_3), 6.98 d (1H, thiazole), 7.28–7.51 m (6H, H_{arom}), 7.80 s (1H, NH), 10.57 br.s (1H, NH). Found, %: N 21.21; S 9.50. $C_{15}H_{15}N_5O_2S$. Calculated, %: N 21.26; S 9.74.

***N*-[4-(4-Methoxyphenyl)-5-methyl-1,3-thiazol-2-yl]-*N'*-(4-methylpyridin-2-yl)urea (IIIc).** Yield 86%, mp 250–252°C. IR spectrum, ν, cm^{-1}: 1685 (C=O), 3280–3350 (N–H). ^1H NMR spectrum, δ, ppm: 2.27 s (3H, CH_3), 2.44 s (3H, CH_3), 3.80 s (3H, OCH_3), 6.95 d (2H, H_{arom}), 7.38 br.s (1H, NH), 7.51–7.56 m (4H, H_{arom}), 8.12 s (1H, H_{arom}), 9.71 br.s (1H, NH). Found, %: N 16.05; S 9.18. $C_{18}H_{18}N_4O_2S_2$. Calculated, %: N 15.81; S 9.05.

***N*-[4-(4-Methoxyphenyl)-5-methyl-1,3-thiazol-2-yl]-3,5-dimethylpiperidine-1-carboxamide (IIId).** Yield 82%, mp 105–106°C. IR spectrum, ν, cm^{-1}: 1690 (C=O); 3300 (N–H). ^1H NMR spectrum, δ, ppm: 0.73–2.22 m (12H, CH_3, CH_2), 2.38 s (3H, CH_3), 3.79 s (3H, OCH_3), 4.16–4.20 m (2H, CH), 6.93 d (2H, H_{arom}), 7.52 d (2H, H_{arom}), 10.65 br.s (1H, NH). Found, %: N 11.89; S 9.05. $C_{19}H_{25}N_3O_2S$. Calculated, %: N 11.69; S 8.92.

***N*-(5-Acetyl-4-methyl-1,3-thiazol-2-yl)-*N'*-(3-trifluoromethylphenyl)urea (IIIe).** Yield 93%, mp >300°C. IR spectrum, ν, cm^{-1}: 1690, 1740 (C=O); 3190–3280 (N–H). ^1H NMR spectrum, δ, ppm: 2.44 s (3H, CH_3), 2.54 s (3H, CH_3), 7.32 d (1H, H_{arom}), 7.51 t (1H, H_{arom}), 7.63 d (1H, H_{arom}), 7.99 s (1H, H_{arom}), 9.27 s (1H, NH), 11.08 br.s (1H, NH). Found, %: N 12.07; S 9.25. $C_{14}H_{12}F_3N_3O_2S$. Calculated, %: N 12.24; S 9.34.

***N*-(5-Acetyl-4-methyl-1,3-thiazol-2-yl)-4-methylpiperazine-1-carboxamide (IIIf).** Yield 80%, mp 195–197°C. IR spectrum, ν, cm^{-1}: 1695, 1745 (C=O); 3260 (N–H). ^1H NMR spectrum, δ, ppm: 2.21 s (3H, CH_3), 2.29–2.32 m (4H, CH_2), 2.40 s (3H, CH_3), 2.53 s (3H, CH_3), 3.50–3.53 m (4H, CH_2), 11.53 br.s (1H, NH). Found, %: N 20.03; S 11.14. $C_{12}H_{18}N_4O_2S$. Calculated, %: N 19.84; S 11.36.

Ethyl 1-(5-acetyl-4-methyl-1,3-thiazol-2-ylcarbamoyl)piperidine-3-carboxylate (IIIg). Yield 73%, mp 222–224°C. IR spectrum, ν, cm^{-1}: 1665, 1690, 1740 (C=O); 3270 (N–H). ^1H NMR spectrum, δ, ppm: 1.21 t (3H, CH_3), 1.44–1.96 m (4H, CH_2), 2.39 s (3H, CH_3), 2.48–2.51 m (1H, CH), 2.53 s (3H, CH_3), 2.99–3.16 m (2H, CH_2), 3.99–4.06 m (1H, CH), 4.07 t (1H, CH), 4.09–4.17 m (1H, CH), 11.37 br.s (1H, NH). Found, %: N 12.61; S 9.35. $C_{15}H_{21}N_3O_4S$. Calculated, %: N 12.38; S 9.45.

***N*-(4-Difluoromethoxyphenyl)-*N'*-(4,5,6,7-tetrahydro-1,3-benzothiazol-2-yl)urea (IIIi).** Yield 89%, mp >300°C. IR spectrum, ν, cm^{-1}: 1700 (C=O), 3290–3330 (N–H). ^1H NMR spectrum, δ, ppm: 1.71–1.77 m (2H, CH_2), 2.36–2.60 m (2H, CH_2), 3.10–3.18 m (4H, CH_2), 7.09 t (1H, CHF_2), 7.11 d (2H, H_{arom}), 7.84 d (2H, H_{arom}), 8.62 br.s (1H, NH), 11.05 br.s (1H, NH). Found, %: N 12.53; S 9.66. $C_{15}H_{15}F_2N_3O_2S$. Calculated, %: N 12.38; S 9.45.

***N*-(1-Methyl-4-phenylbutyl)-*N′*-(6-methyl-4,5,6,7-tetrahydro-1,3-benzothiazol-2-yl)urea (IIIj).** Yield 76%, mp 148–150°C. IR spectrum, ν, cm^{-1}: 1705 (C=O), 3270–3310 (N–H). ^1H NMR spectrum, δ, ppm: 1.02–2.12 m (19H, CH_3, CH_2, CH), 3.64–3.68 m (1H, CH), 6.52–6.54 m (1H, NH), 7.20–7.36 m (5H, H_{arom}), 9.76 br.s (1H, NH). Found, %: N 11.72; S 9.14. $C_{20}H_{27}N_3OS$. Calculated, %: N 11.75; S 8.97.

***N*-(6-Methyl-4,5,6,7-tetrahydro-1,3-benzothiazol-2-yl)-*N′*-(3-morpholinopropyl)urea (IIIk).** Yield 82%, mp 153–155°C. IR spectrum, ν, cm^{-1}: 1690 (C=O), 3250–3310 (N–H). ^1H NMR spectrum, δ, ppm: 1.06–3.15 m (20H, CH_3, CH_2, CH), 3.54–3.57 m (4H, CH_2), 6.54 br.s (1H, NH), 9.97 br.s (1H, NH). Found, %: N 16.50; S 9.31. $C_{16}H_{26}N_4O_2S$. Calculated, %: N 16.55; S 9.47.

***N*-(6-Methyl-4,5,6,7-tetrahydro-1,3-benzothiazol-2-yl)-*N′*-(3-pyridyl)urea (IIIl).** Yield 91%, mp >300°C. IR spectrum, ν, cm^{-1}: 1695 (C=O), 3270–3350 (N–H). ^1H NMR spectrum, δ, ppm: 1.04 d (3H, CH_3), 1.10–2.49 m (7H, CH_2, CH), 7.28 t (1H, H_{arom}), 7.96 d (1H, H_{arom}), 8.17 d (1H, H_{arom}), 8.56 s (1H, H_{arom}), 8.91 s (1H, NH), 10.76 br.s (1H, NH). Found, %: N 19.62; S 10.93. $C_{14}H_{16}N_4OS$. Calculated, %: N 19.43; S 11.12.

The IR spectra were recorded in KBr on a UR-20 spectrometer. The ^1H NMR spectra were obtained on a Varian Gemini instrument (300 MHz) from solutions in DMSO-d_6 using TMS as internal reference.

REFERENCES

1. Engelhart, J.E., FRG Patent no. 1932699, 1970; *Chem. Abstr*., 1970, vol. 72, p. 121514r.
2. Engelhart, J.E., FRG Patent no. 2116956, 1972; *Chem. Abstr*., 1972, vol. 76, no. 141534h.
3. Singer, M.S., US Patent no. 4012225, 1977; *Chem. Abstr*., 1977, vol. 87, no. 5673s.
4. Wu, C.C. and Krenzer, J., US Patent no. 4086240, 1978; *Chem. Abstr*., 1978, vol. 89, no. 109486b.
5. Yamamoto, Y., Nakamura, H., Yoda, R., Kaneko, N., and Usuba, R., *Kyoritsu Yakka Daigaku Nempo*, 1966, vol. 11, p. 42; *Chem. Abstr*., 1968, vol. 68, p. 10507f.
6. Wilhelm, M., Marguartt, F.-H., Meier, K., and Schmidt, P., *Helv. Chim. Acta*., 1966, vol. 49, p. 2443.
7. Romeo, G., Salerno, L., Milla, P., Siracusa, M., Cattel, L., and Russo, F., *Pharmazie*, 1999, vol. 54, p. 19.
8. Wityak, J., Das, J., Moguiv, R.V., Shen, Zh., Lin, J., Chen, P., Doweyko, A.M., Suhong, P., Shen, D.R., Fong, Q., Fex, H.F., Schieven, G.L., Kanner, S.B., and Barrish, J.C., *Bioorg. Med. Chem. Lett*., 2003, vol. 13, p. 4007.
9. Venkatachalan, T.K. and Uckun, F.M., *Synth. Commun*., 2004, vol. 34, p. 2451.
10. Dolpiaz, A., Ferreti, M.E., Vertuani, G., Traniello, S., Scatturini, A., and Spisani, S., *Eur. J. Pharmacol*., 2002, vol. 436, p. 187.
11. Iriepa, J., Gil-Alberdi, B., Galves, E., Bellunato, J., and Cormona, P., *J. Mol. Struct*., 1997, vol. 408, p. 487.
12. Lombardino, J.G., Anderson, S.L., and Norris, C.P., *J. Heterocycl. Chem*., 1978, vol. 15, p. 655.