Russian Journal of Organic Chemistry, Vol. 41, No. 8, 2005, pp. 1240–1241. Translated from Zhurnal Organicheskoi Khimii, Vol. 41, No. 8, 2005, pp. 1261–1262.
Original Russian Text Copyright © 2005 by Vovk, Sukach.

SHORT COMMUNICATIONS

α-Chlorobenzyl Isocyanates in a New Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-ones

M.V. Vovk and V.A. Sukach

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

Received March 17, 2005

5-Functionally substituted 3,4-dihydropyrimidin-2(1*H*)-ones constitute a unique heterocyclic system possessing versatile pharmacological properties [1–3]. The three-component cyclocondensation of 1,3-dicarbonyl compounds with aldehydes and urea discovered by Biginelli [4] in 1893 is a traditional procedure for preparation of these compounds that is successfully used up till now. The other synthetic methods described [5–7] as a rule are modifications of this reaction.

We developed a new synthetic approach to compounds of the 3,4-dihydropyrimidine series based on the condensation of sufficiently accessible reagents: α-chlorobenzyl isocyanates **Ia–If** [8] and enamines **IIa–IIc**. We demonstrated that isocyanates **Ia–If** reacted with enamines **IIa–IIc** in toluene at room temperature affording in good yields 3,4-dihydropyrimidin-2(1*H*)-ones **IIIa–IIIf**. The discovered reaction is a new [C=N–C] + [C=C–N] method [9, 10] of building up the pyrimidine ring. Compounds **III** might form via two alternative pathways; however taking into account previous results on reaction of 1-aryl-1-chloro-2,2,2-trifluoroethyl isocyanates with ethyl β-*N*-methylaminocrotonate [11] it is presumable that the reaction occurs through an intermediate formation of isocyanatealkylated products **A**.

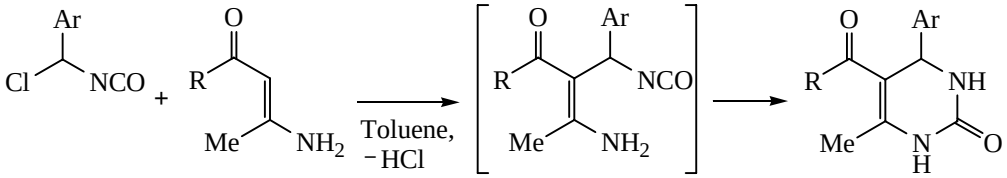
α-Chlorobenzyl isocyanates **Ia–If** were prepared by procedure [8].

(2-Fluorophenyl)chloromethyl isocyanate (Ib). Yield 59%, bp 120–124°C (12 mm Hg). IR spectrum (CH_2Cl_2), cm^{-1}: 2265 (N=C=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 6.70 s (1H, CH), 7.10–7.65 m ($4H_{arom}$). Found, %: C 51.60; H 2.79; N 7.64. C_8H_5ClFN. Calculated, %: C 51.78; H 2.72; N 7.55.

(3-Bromophenyl))chloromethyl isocyanate (Ic). Yield 81%, bp 141–146°C (0.2 mm Hg). IR spectrum (CH_2Cl_2), cm^{-1}: 2270 (N=C=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 6.61 s (1H, CH), 7.12–7.68 m ($4H_{arom}$). Found, %: C 38.75; H 1.99; N 5.60. C_8H_5BrClN. Calculated, %: C 38.98; H 2.04; N 5.68.

(4-Chlorophenyl)chloromethyl isocyanate (Id). Yield 72%, bp 126–130°C (0.3 mm Hg). IR spectrum (CH_2Cl_2), cm^{-1}: 2265 (N=C=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 6.45 s (1H, CH), 7.36–7.50 m ($4H_{arom}$). Found, %: C 47.73; H 2.55; N 6.87. $C_8H_5Cl_2N$. Calculated, %: C 47.56; H 2.49; N 6.93.

3,4-Dihydropyrimidin-2(1*H*)-ones IIIa–IIIf. To a solution of 5 mmol of α-chlorobenzylisocyanate **Ia–If** in 20 ml of anhydrous toluene was added 5 mmol of



Ia–If **IIa–IIc** **A** **IIIa–IIIf**

I, Ar = C_6H_5 (**a**), 2-F-C_6H_4 (**b**), 3-Br-C_6H_4 (**c**), 4-Cl-C_6H_4 (**d**), 4-Br-C_6H_4 (**e**), 4-NO_2-C_6H_4 (**f**); **II**, R = Me (**a**), MeO (**b**), EtO (**c**); **III**, R = Me, Ar = 2-F-C_6H_4 (**a**), 3-Br-C_6H_4 (**b**); R = MeO, Ar = 4-Cl-C_6H_4 (**c**), 4-NO_2-C_6H_4 (**d**); R = EtO, Ar = C_6H_5 (**e**), 4-Br-C_6H_4 (**f**).

1070-4280/05/4108-1240©2005 Pleiades Publishing, Inc.

enamine **IIa–IIc**, and the mixture was stirred for 1 h at room temperature. Then the precipitate was filtered off and recrystallized from ethanol.

5-Acetyl-6-methyl-4-(2-fluorophenyl)-3,4-dihydropyrimidin-2(1*H*)-one (IIIa). Yield 68%, mp 235–237°C. IR spectrum (KBr), cm^{-1}: 3200 (NH), 1690, 1650 (C=O). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.12 s (3H, CH_3), 2.29 s (3H, CH_3), 5.23 d (1H, CH, *J* 2.1 Hz), 7.22–7.40 m ($4H_{arom}$), 7.81 d (1H, NH, *J* 2.1 Hz), 9.21 s (1H, NH). Found, %: C 50.39; H 4.17; N 9.01. $C_{13}H_{13}BrN_2O_2$. Calculated, %: C 50.51; H 4.24; N 9.06.

5-Acetyl-4-(3-bromophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (IIIb). Yield 65%, mp 248–250°C. IR spectrum (KBr), cm^{-1}: 3190 (NH), 1690, 1660 (C=O). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.06 s (3H, CH_3), 2.29 s (3H, CH_3), 5.51 d (1H, CH, *J* 2.0 Hz), 7.12–7.48 m ($4H_{arom}$), 7.68 d (1H, NH, *J* 2.0 Hz), 9.20 s (1H, NH). Found, %: C 62.95; H 5.33; N 11.34. $C_{13}H_{13}FN_2O_2$. Calculated, %: C 62.90; H 5.28; N 11.28.

6-Methyl-5-methoxycarbonyl-4-(4-chlorophenyl)-3,4-dihydropyrimidin-2(1*H*)-one (IIIc). Yield 66%, mp 178–180°C [12].

6-Methyl-5-methoxycarbonyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1*H*)-one (IIId). Yield 69%, mp 213–215°C [12].

6-Methyl-4-phenyl-5-ethoxycarbonyl-3,4-dihydropyrimidin-2(1*H*)-one (IIIe). Yield 71%, mp 202–204°C [12].

4-(4-Bromophenyl)-6-methyl-5-ethoxycarbonyl-3,4-dihydropyrimidin-2(1*H*)-one (IIIf). Yield 73%, mp 195–197°C [13].

IR spectra were recorded on UR-20 instrument. ^1H NMR spectra were registered on spectrometer Varian-Gemini (300 MHz), internal reference TMS.

REFERENCES

1. Folkers, K. and Johnson, T.B., *J. Am. Chem. Soc.*, 1933, vol. 55, p. 3781.
2. Kappe, C.O., *Tetrahedron*, 1993, vol. 49, p. 6937.
3. Kappe, C.O., *Acc. Chem. Res.*, 2000, vol. 33, p. 879.
4. Biginelli, P., *Gazz. Chim. Ital.* 1893, vol. 23, p. 360.
5. O'Reilly, B.C. and Atwal, K. S., *Heterocycles*, 1987, vol. 26, p. 1185.
6. Atwal, K.S., O'Reilly, B. C., Gougoutas, J.Z., and Malley, M.F., *Heterocycles*, 1987, vol. 26, p. 1189.
7. Shutalev, A.D., Kishko, E.A., Sivova, N.V., and Kuznetsov, A.Yu., *Molecules*, 1998, vol. 3, p. 100.
8. Sinitsa, A.D., Bonadyk, S.V., and Markovskii, L.N. , *Zh. Org. Khim.*, 1978, vol. 14, p. 1107.
9. Vovk, M.V., Lebed', P.S., Sukach, V.A., and Kornilov, M.Yu., *Zh. Org. Khim.*, 2003, vol. 39, p. 1852.
10. Vovk, M.V., Lebed', P.S., Pirozhenko, V.V., and Tsymbal, I.F., *Zh. Org. Khim.*, 2004, vol. 40, p. 1715.
11. Vovk, M.V. and Pirozhenko, V.V., *Khim. Geterotsikl. Soed.*, 1994, p. 96.
12. Fu, N.-Y., Yuan, Y.-F, Cao, Z., Wang, S.-W., Wang, J.-T., and Peppe, C., *Tetrahedron*, 2002, vol. 58, p. 4801.
13. Reddy, K.R., Reddy, C.V., Manesh, M., Raju, P.V.K., and Reddy, V.V.N., *Tetrahedron Lett.*, 2003, vol. 44, p. 8173.