ISSN 1070-4280, Russian Journal of Organic Chemistry, 2007, Vol. 43, No. 3, pp. 471–473. © Pleiades Publishing, Ltd., 2007.
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SHORT COMMUNICATIONS

α-Aminoazoles in Syntheses of Heterocycles. 3(5)-Aminopyrazole-4-carbonitriles in the Synthesis of Pyrazolo[1,5-*a*]pyrimidines

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Received September 16, 2006

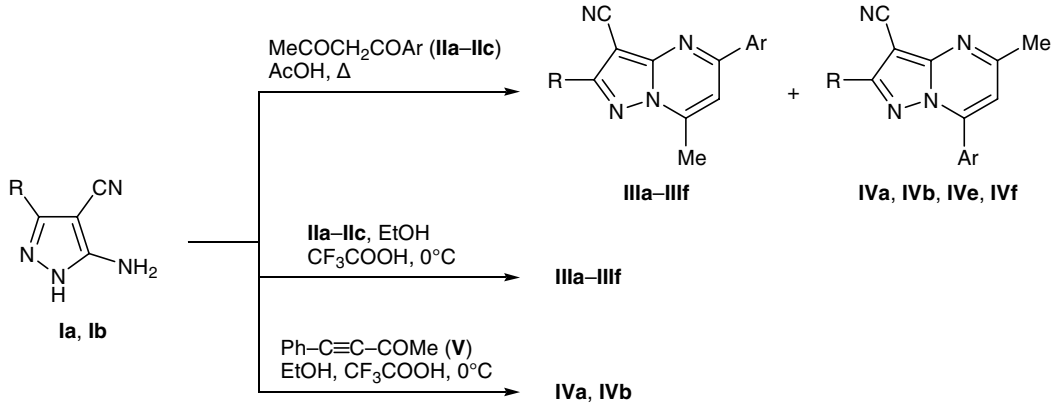
DOI: 10.1134/S1070428007030281

Broad spectrum of biological activity of functionally substituted pyrazolopyrimidines stimulates development of new methods for the synthesis of these compounds [1–3]. In the past 10–15 years, new sedative and soporific medical agents have been found among pyrazolopyrimidine derivatives; among these, Zaleplon {*N*-[3-(3-cyanopyrazolo[1,5-*a*]pyrimidin-7-yl)phenyl]-*N*-ethylacetamide}is one of the most efficient [4, 5].

We have developed a procedure for the regioselective synthesis of substituted 7-aryl-5-methylpyrazolo-[1,5-*a*]pyrimidine-3-carbonitriles that are structurally related to Zaleplon. The procedure is based on cyclocondensation of 3(5)-aminopyrazole-4-carbonitriles with 1-arylbutane-1,3-diones in ethanol at a temperature not exceeding 0°C in the presence of trifluoroacetic acid as catalyst. The only products of these reactions are 7-aryl-5-methylpyrazolo[1,5-*a*]pyrimidine-3-carbonitriles **IIIa**–**IIIf**; they are isolated in high yields as high-melting crystalline substances.

Reactions of unsymmetrical 1,3-diketones with 3(5)-aminopyrazoles [6, 7] often lead to the formation of mixtures of two regioisomeric pyrazolo[1,5-*a*]pyrimidines due to comparable reactivities of the two electrophilic centers in the initial diketone. Reactions of benzoylacetones **IIa**–**IIc** with 3(5)-aminopyrazole-4-carbonitriles **Ia** and **Ib**, performed according to the procedures described in [6, 7] (fusion or heating in acetic acid or ethanol), give almost inseparable mixtures of regioisomeric pyrazolopyrimidines **III** and **IV** (fraction of **IV** ~10–30%). We have succeeded in obtaining compounds **IVa** and **IVb** as the only products by reaction of 3(5)-aminopyrazole-4-carbonitriles **Ia** and **Ib** with 4-phenylbut-3-yn-2-one (**V**), following the procedure described by us previously [8].

The structure of regioisomers **IIIa**, **IIIb**, **IVa**, and **IVb** was determined on the basis of the ^{1}H and ^{13}C NMR data, taking into account characteristic chemical shifts of protons and carbon atom of the methyl group and C^{i} in the phenyl group of both compounds, δ_C, ppm: 5-CH_3 ~25, 7-CH_3 ~17, 5-C^{i} ~136.5, 7-C^{i} ~131 [8, 9]. In all cases, the 5-CH_3 signal appears in a stronger field than that from 7-CH_3 by about 0.1 ppm.



I, R = H (**a**), Me (**b**); **II**, Ar = Ph (**a**), 4-*i*-$PrOC_6H_4$ (**b**), 4-ClC_6H_4 (**c**); **III**, **IV**, Ar = Ph, R = H (**a**), Me (**b**), Ar = 4-*i*-$PrOC_6H_4$, R = H (**c**), Me (**d**), Ar = 4-ClC_6H_4, R = H (**e**), Me (**f**).

7-Aryl-5-methylpyrazolo[1,5-*a*]pyrimidine-3-carbonitriles IIIa–IIIf (*general procedure*). A solution of 2.5 mmol of benzoylacetone **IIa–IIc** in 3 ml of ethanol was added to a solution of 2.5 mmol of aminopyrazole **Ia** or **Ib** in 2 ml of ethanol containing 3 drops of trifluoroacetic acid at a temperature not exceeding 0°C. The mixture was stirred at 0°C until the reaction was complete (TLC, Silufol UV-254), and the precipitate was filtered off, treated with boiling ethanol, and filtered off again.

5-Methyl-7-phenylpyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (IIIa). Yield 85%, mp 214°C. ^{1}H NMR spectrum, δ, ppm: in $CDCl_3$: 2.76 s (3H, CH_3), 7.03 s (1H, 6-H), 7.59-7.90 m (5H, Ph), 8.34 s (1H, 2-H); in DMSO-d_6: 2.69 s (3H, CH_3), 7.42 s (1H, 6-H), 7.59–8.06 m (5H, Ph), 8.69 s (1H, 2-H). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 25.25 (CH_3), 81.15 (CN), 112.22 (C^6), 114.39 (C^3), 129.33, 130.32 (C^i), 130.45, 133.32 (Ph), 147.40 (C^2), 147.70 (C^7), 151.62 (C^{3a}), 164.75 (C^5). Found, %: C 71.68; H 4.55. $C_{14}H_{10}N_4$. Calculated, %: C 71.78; H 4.30.

2,5-Dimethyl-7-phenylpyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (IIIb). Yield 81%, mp 179°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.55 (3H, 2-CH_3), 2.76 (3H, 5-CH_3), 7.30 (1H, 6-H), 7.58–8.05 (Ph). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 14.15 (2-CH_3), 25.14 (5-CH_3), 80.99 (CN), 111.59 (C^6), 114.32 (C^3), 129.25, 130.32 (C^i), 132.15 (Ph), 146.77 (C^7), 152.03 (C^{3a}), 157.34 (C^2), 164.03 (C^5). Found, %: C 72.40; H 4.95. $C_{15}H_{13}N_4$. Calculated, %: C 72.56; H 4.87.

7-(4-Isopropoxyphenyl)-5-methylpyrazolo-[1,5-*a*]pyrimidine-3-carbonitrile (IIIc). Yield 87%, mp 108°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.37 d [6H, $(CH_3)_2CH$, *J* = 5.9], 2.70 (3H, 5-CH_3), 4.74 sept (1H, CH, *J* = 5.9), 7.25 (1H, 6-H), 7.03 d and 8.08 d (2H each, C_6H_4). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 22.55 [$(CH_3)_2CH$], 25.17 (5-CH_3), 70.31 (OCH), 81.32 (CN), 110.65 (C^6), 113.90 (C^3), 115.87, 121.63, 132.23 (C^i), 161.09 (C_6H_4), 147.13 (C^2), 151.77 (C^{3a}), 147.13 (C^7), 163.86 (C^5). Found, %: C 69.96; H 5.67. $C_{17}H_{16}N_4O$. Calculated, %: C 69.85; H 5.52.

7-(4-Isopropoxyphenyl)-2,5-dimethylpyrazolo-[1,5-*a*]pyrimidin-3-carbonitrile (IIId). Yield 82%, mp 112°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.38 d [6H, $(CH_3)_2CH$, *J* = 5.9], 2.54 (3H, 2-CH_3), 2.66 (3H, 5-CH_3), 4.74 sept (1H, CH, *J* = 5.9), 7.25 (1H, CH), 7.03 d and 8.07 d (2H each, C_6H_4). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 14.13 (2-CH_3), 22.57 [$(CH_3)_2CH$], 25.07 (5-CH_3), 70.30 (OCH), 81.0 (CN), 110.19 (C^6), 114.12 (C^3), 115.84, 121.78, 132.15 (C^i), 160.97 (C_6H_4), 146.55 (C^2), 152.25 (C^{3a}), 157.06 (C^7), 163.34 (C^5). Found, %: C 70.41; H 6.09. $C_{18}H_{18}N_4O$. Calculated, %: C 70.57; H 5.92.

7-(4-Chlorophenyl)-5-methylpyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (IIIe). Yield 92%, mp 292°C (decomp.). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.70 (3H, CH_3), 7.47 (1H, 6-H), 7.67 d and 8.12 d (C_6H_4), 8.68 (1H, 2-H). Found, %: C 62.40; H 3.52. $C_{14}H_9ClN_4$. Calculated, %: C 62.58; H 3.38.

7-(4-Chlorophenyl)-2,5-dimethylpyrazolo[1,5-*a*]-pyrimidine-3-carbonitrile (IIIf). Yield 90%, mp 207°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.58 (3H, 2-CH_3), 2.71 (3H, 5-CH_3), 6.94 (1H, 6-H), 7.56 d and 7.97 d (4H, C_6H_4). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.18 (2-CH_3), 25.33 (5-CH_3), 82.21 (CN), 110.60 (C^6), 113.94 (C^3), 128.58, 129.56, 131.20 (C^i), 138.33 (C_6H_4), 146.02 (C^7), 152.13 (C^{3a}), 158.26 (C^2), 163.36 (C^5). Found, %: C 63.50; H 4.05. $C_{15}H_{11}ClN_4$. Calculated, %: C 63.72; H 3.92.

7-Methyl-5-phenylpyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (IVa). Yield 90%, mp 164°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.86 s (3H, CH_3), 7.54 m and 8.24 m (5H, Ph), 7.85 (1H, 6-H), 8.58 (1H, 2-H). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 17.68 (CH_3), 82.47 (CN), 108.47 (C^6), 113.88 (C^3), 128.40, 129.60, 131.94, 136.36 (C^i) (Ph), 147.90 (C^7), 148.92 (C^{3a}), 150.60 (C^2), 159.26 (C^5). Found, %: C 71.60; H 4.50. $C_{14}H_{10}N_4$. Calculated, %: C 71.78; H 4.30.

2,7-Dimethyl-5-phenylpyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (IVb). Yield 85%, mp 213°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.52 (3H, 2-CH_3), 2.76 (3H, 7-CH_3), 7.70 (1H, 6-H), 7.58–8.02 (Ph). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 14.15 (2-CH_3), 17.63 (7-CH_3), 81.72 (CN), 107.90 (C^6), 114.30 (C^3), 128.21, 129.63, 131.92, 136.30 (C^i) (Ph), 148.48 (C^7), 150.60 (C^{3a}), 157.94 (C^2), 158.67 (C^5). Found, %: C 72.49; H 4.92. $C_{15}H_{13}N_4$. Calculated, %: C 72.56; H 4.87.

5-(4-Chlorophenyl)-7-methylpyrazolo[1,5-*a*]-pyrimidine-3-carbonitrile (IVe). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.85 (3H, CH_3), 7.65 d and 8.28 d (C_6H_4), 7.95 (1H, 6-H), 8.78 (1H, 2-H).

5-(4-Chlorophenyl)-2,7-dimethylpyrazolo[1,5-*a*]-pyrimidine-3-carbonitrile (IVf). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.65 (3H, 2-CH_3), 2.87 (3H, 7-CH_3), 7.29 (1H, 6-H), 7.50 d and 8.13 d (4H, C_6H_4).

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-300 spectrometer at 300 and 75 MHz,

respectively, using $CDCl_3$ and DMSO-d_6 as solvents. Signals from protons in compounds **IVe** and **IVf** were identified in the ^1H NMR spectrum of the corresponding isomer mixture **III/IV**. Aminopyrazoles **Ia** and **Ib** were synthesized according to the procedure reported in [10]. Pyrazolo[1,5-*a*]pyrimidines **IVa** and **IVb** were prepared as described in [8].

REFERENCES

1. Chen, Ch., Wilcoxen, K.M., Huang, Ch.Q., McCarthy, J.R., Chen, T., and Grigoriadis, D.E., *Bioorg. Med. Chem. Lett*., 2004, vol. 14, p. 3669.
2. Gopalsamy, A., Yang, H., Ellingboe, J.W., Tsou, H., Zhang, N., Honores, E., Powel, D., Miranda, M., McGinnis, J.P., and Rabindran, S.K., *Bioorg. Med. Chem. Lett*., 2005, vol. 15, p. 1591.
3. Zaharan, M.A., El-Sharief, A.M.Sh., El-Gaby, M.S.A., Ammar, Y.A.A., and El-Said, U.H., *Farmaco*, 2001, vol. 56, p. 277.
4. George, C.F.P., *Lancet*, 2001, vol. 357, p. 1623.
5. Moore, K.A., Zemrus, T.L., Ramcharitar, V., Levine, B., and Fowler, D.R., *Forensic Sci. Int*., 2003, vol. 134, p. 120.
6. Elnagdi, M.H., Elmoghayar, M.R.H., and Elgemeie, G.E.H., *Advances in Heterocyclic Chemistry*, Katritzky, A.R., Ed., New York: Academic, 1987, vol. 41, p. 319.
7. Maquestiau, A., Target, H., and Van den Eyden, J.-J., *Bull. Soc. Chim. Belg*., 1992, vol. 101, p. 131.
8. Petrov, A.A., Emelina, E.E., and Firsov, A.V., *Russ. J. Org. Chem*., 2000, vol. 36, p. 1027.
9. Emelina. E.E., Petrov, A.A., and Firsov, A.V., *Russ. J. Org. Chem*., 2001, vol. 37, p. 852.
10. Robins, R.K., *J. Am. Chem. Soc*., 1956, vol. 78, p. 784.