Synthesis of new bispidine-type compounds starting from Guareschi imides

Elena A. Chigorina[1],* and *Victor V. Dotsenko*[2]

[1]ChemDiv Research Institute (CDRI), Rabochaya St. 2-a, Moscow Region, Khimki
[2]ChemEx Laboratory, Vladimir Dal' East Ukrainian National University, Molodezhny 20A, Lugansk

The reaction of 1-cyanoacetyl-3,5-dimethylpyrazole with 2-cyanoacrylamides in the presence of Et_3N leads to triethylammonium 3,5-dicyano-6-oxo-1,4,5,6-tetrahydropyridine-2-olates (salts of Guareschi imides). The latter reacted with primary amines RNH_2 and an excess of HCHO to give triethylammonium salts of 7-R-2,4-dioxo-3,7-diazabicyclo[3.3.1]nonane-1,5-dicarbonitriles. When treated with HCl or alkyl halides, the salts afforded corresponding 3-R- or 3,7-disubstituted bispidines.

Keywords: cyanoacetylpyrazole, Guareschi imides, diazabicyclononanes, bispidines, Mannich reaction.

Introduction

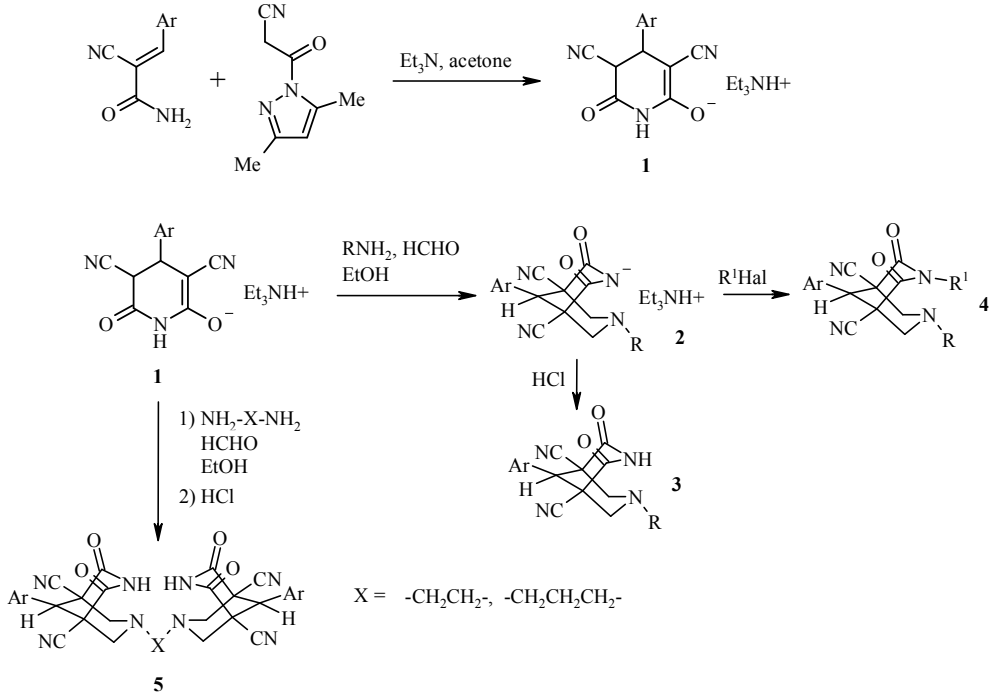
2,6-Dioxopiperidin-3,5-dicarbonitriles (also known as Guareschi imides) which are easily accessible by condensation of ketones, cyanoacetic ester and ammonia [1-3], during its more than a century's history have proved to be suitable reagents for synthesis of glutarimide derivatives, 3,3-disubstituted glutaric acids, pyridine-2(1*H*)-ones, etc. A survey of literature reveals the only way to obtain bispidines (derivatives of 3,7-diazabicyclo[3.3.1]nonane) starting from Guareschi imides based on an acid hydrolysis of the nitrile groups [4-8]. Such compounds are of interest as intermediates in the synthesis of anti-ischemic agents [9] and sparteine-type alkaloids [10].

Previously we have described a convenient synthesis of salts of 4-monosubstituted Guareschi imides by reaction of 3-aryl-2-cyanoacrylamides with 1-cyanoacetyl-3,5-dimethylpyrazole [11, 12]. These compounds, as well as other long time known 2,6-dioxopiperidin-3,5-dicarbonitriles, are of interest as C-3/C-5-dinucleophilic substrates to prepare bispidines by double Mannich-type aminomethylation. The Mannich reaction of 3,5-dinucleophilic pyridine species is one of the most common methods for synthesis of 3,7-diazabicyclo[3.3.1]nonane derivatives [13, 14]. However, no data on the aminomethylation of Guareschi imides was reported in the literature to date.

We found that the reaction of glutarimide salts **1** with primary amines and an excess of HCHO proceeds under mild conditions and results in the formation of triethylammonium salts of 2,4-dioxo-3,7-diazabicyclo[3.3.1]nonanes (bispidinates) **2**. Upon treatment with acids, bispidinates **2** afforded expected bispidines **3**. When

* Author to whom correspondence should be addressed.

treated with alkyl halides, bispidinates undergo N-alkylation to give diazobicyclononanes **4**. Finally, the reaction of salts **1** with primary α,ω-diamines under Mannich conditions followed by acidification gave compounds **5**, albeit in low yields.



These transformations demonstrate the first example for the synthesis of 3,7-diazabicyclo[3.3.1]nonanes starting from Guareschi imides. The structure of compounds **2** and **3a,b** was confirmed by ^{1}H NMR spectroscopy, IR spectroscopy, HPLC-MS and elemental analysis. Optimization of the conditions, the scope and limitations of the method will be reported elsewhere.

Experimental

^{1}H NMR spectra were recorded on Bruker DPX-400 (400.40 MHz) in DMSO-d_6, with TMS as an internal standard. IR spectra were recorded on an Thermo Nicolet Magna IR 750 FTIR Spectrometer (KBr). HPLC-MS analysis was performed on liquid chromatograph Shimadzu LC-10AD with detectors Shimadzu SP D-10A UV-Vis (254 nm) and Sedex 75 ELSD, combined with a PE SCIEX API 150EX mass spectrometer, ionization method ES-API. Elemental analysis was performed on Carlo-Erba 1106 elemental analyser. The purity of all obtained compounds was checked by TLC on Sorbfil PTLC-AF-B-UV plates with acetone–hexane (1:1) as eluent; spots were visualized with iodine vapors and UV light. Melting points were determined on Electrothermal Mel-Temp 3.0 apparatus and are uncorrected. Starting tetrahydropyridine-2-olates **1** were prepared by known methods [11, 12].

Triethylammonium salts of 2,4-dioxo-3,7-diazabicyclo[3.3.1]nonanes (2), bispidines (3, 5). **General procedure.** A 50 ml beaker was charged with 1.05 mmol of tetrahydropyridine-2-olate **1**, then 1.1 mmol of primary amine (0.55 mmol of diamine), 10 ml of 96% EtOH, and 1.0 ml (13.3 mmol) of 37% HCHO were

added under vigorous stirring. The solution was gently boiled for 1 min and then stirred for 3-4 h at ~20 °C. The mixture was kept for 24-72 h at ambient temperature, the precipitate was filtered off, washed with EtOH and ether. Bispidines **3,5** were obtained when the reaction mixture was treated with 3-5 ml of 96% EtOH and 10% aq. HCl until pH=2 was reached. After 48 hours, the precipitate was filtered off, washed with 50% EtOH, ether and dried.

Alkylation of bispidinates (2). General procedure. To a clear solution of 1.0 mmol of salt **2** in 2.0 mL of DMF, 1.0 mmol of alkyl halide was added. The mixture was kept for 72 h at 20 °C, diluted with water, the obtained solid was collected and recrystallized from EtOH to give N-alkyl derivatives **4**.

Representative spectral data. Triethylammonium salt of 7-benzyl-9-(2-chlorophenyl)-2,4-dioxo-3,7-diazabicyclo[3.3.1]nonane-1,5-dicarbonitrile (2, Ar = 2-ClC$_6$H$_4$, R = CH$_2$Ph). Yield 69%, colorless crystals. FTIR-spectrum (KBr), ν, cm^{-1}: 3441 (N-H), 2240 (C≡N), 1718, 1661 (C=O), 1608 (C=C). ^{1}H NMR spectrum (400 MHz, DMSO-d$_6$), δ, ppm: 1.07 (9H, t, ^{3}J = 7.1, Et), 2.81 (6H, q, ^{3}J = 7.1, Et), 2.99 (2H, d , ^{2}J = 10.8, H-6, H-8), 3.33 (2H, d, ^{2}J = 10.8, H-6, H-8), 3.72 (2H, br.s, CH$_2$Ph); 4.36 (1H, c, H-9), 7.22-7.45 (8H, m, H-Ar); 7.60-7.62 (1H, m, H-Ar). Mass spectrum, *m/z* (ES-API): 102.3 [Et$_3$NH]$^+$, 405.3 [(M-101) + H]$^+$, 809.0 [2(M-101) + H]$^+$. Found, %: C 66.50; H 6.49; N 13.92. $C_{28}H_{32}ClN_5O_2$ (M 506.04). Calculated, %: C 66.46; H 6.37; N 13.84.

References

1. I. Guareschi, *Chem. Zbl*., **69** Pt. II, 544 (1898).
2. I. Guareschi, E. Grande, *Chem. Zbl*., **70** Pt. 2, 439 (1899).
3. I. Guareschi, *Chem. Zbl*., **72** Pt. I, 579 (1901).
4. J. F. Thorpe, A. S. Wood, *J. Chem. Soc., Trans*., **103**, 1586 (1913).
5. S. M. McElvain, D. H. Clemens, *J. Am. Chem. Soc*., **80**, 3915 (1958).
6. G. J. Handley, E. R. Nelson, T. C. Somers, *Austr. J. Chem*., **13**, 129 (1960).
7. L. M. Rice, C. F. Geschickter, C. H. Grogan, *J. Med. Chem*., **6**, 388 (1963).
8. Y. Xu, L.Xie, B. Han, G. D. Maynard, B. L. Chenard, A. J. Staab, Pat. WO2009/097405 (06.08.2009); Avail. URL: http://worldwide.espacenet.com/
9. U. Schön, J. Antel, R. Brückner, J. Messinger, R. Franke, A. Gruska, *J. Med. Chem*., **41**, 318 (1998).
10. N. R. Norcross, J. P. Melbardis, M. Ferris Solera, M. A. Sephton, C. Kilner, L. N. Zakharov, P. C. Astles, S. L. Warriner, P. R. Blakemore, *J. Org. Chem*., **73**, 7939 (2008).
11. E. Chigorina, V. Dotsenko, in *Proceedings of the 15th Int. Electron. Conf. Synth. Org. Chem.*, 1-30 November 2011; Sciforum Electronic Conferences Series, 2011. Avail. URL: http://www.sciforum.net/presentation/702/
12. E. A. Chigorina, V. V. Dotsenko, S. G. Krivokolysko, *Chem. Heterocycl. Compds*, Vol. 47, No. 7, 913 (2011).
13. N. S. Zefirov, S. V. Rogozina, *Russ. Chem. Rev.,* 1973, **42** (3), 190 (1973).
14. R. Jeyaraman, S. Avila, *Chem. Rev.*, **81**, 149 (1981).