Chemistry of Heterocyclic Compounds, Vol. 47, No. 7, October 2011 (Russian original Vol. 47, No. 7, July, 2011)

NEW APPROACH TO THE SYNTHESIS OF 4-ARYL-3,5-DICYANO-6-OXO-1,4,5,6-TETRAHYDROPYRIDIN-2-OLATES (SALTS OF GUARESCHI IMIDES)

E. A. Chigorina[1], V. V. Dotsenko[2]*, and S. G. Krivokolysko[2]

Keywords: 4-aryl-2,6-dioxopiperidine-3,5-dicarbonitriles, 1-cyanoacetyl-3,5-dimethylpyrazole, Guareschi imides, 4-(2-chlorophenyl)-3,5-dicyano-6-oxo-1,4,5,6-tetrahydropyridin-2-olate, Michael reaction.

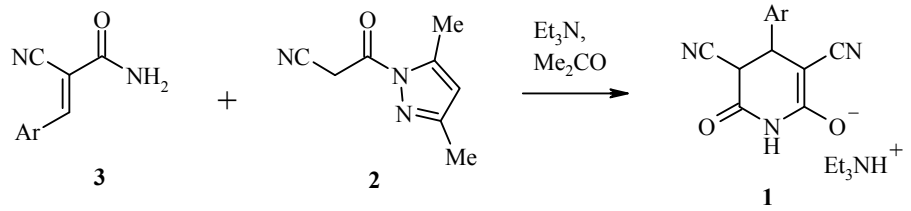
Derivatives of 2,6-dioxopiperidine-3,5-dicarbonitrile (Guareschi imides) are of practical interest as anti-convulsants, sedatives, and analgesics [1] as well as promising building blocks for the preparation of bispidine (3,7-diazabicyclo[3.3.1]nonane) derivatives [2, 3] and biologically active compounds [4–6]. The most convenient method for the preparation of these compounds is the Guareschi reaction, namely, the reaction of ethyl cyanoacetate with ketones and ammonia [7–11] or, in an alternative variant, the reaction of 2-cyanoacrylates with cyanoacetamide [4, 6, 12, 13]. The classical Guareschi reaction has its disadvantages. The yields and reaction times vary. Also, there are limitations related to the need to use only ketones as the carbonyl components. Guareschi imides are known to undergo facile oxidation by atmospheric oxygen [14]. When aldehydes are used in this reaction instead of ketones, the final products are only the oxidation products, namely, 4-alkyl- or 4-aryl-6-hydroxy-2-oxo-1,2-dihydropyridine-3,5-dicarbonitriles or their salts [15–19]. Only a few examples of the preparation of 4-aryl-2,6-dioxopiperidine-3,5-dicarbonitriles or their salts have been reported [1, 20, 21]. As a rule, either the products are obtained in low yield or the methods require the use of exotic reagents such as Li_3N as the source of NH_3.

We have found that the salt of the Guareschi imide, triethylammonium 4-(2-chlorophenyl)-3,5-dicyano-6-oxo-1,4,5,6-tetrahydropyridine-2-olate (**1**), may be synthesized under mild conditions by the Michael reaction of readily available 1-cyanoacetyl-3,5-dimethylpyrazole **2** [22, 23] with 3-(2-chlorophenyl)-2-cyanoacrylamide **3**. Pyridinolate **1** is formed in 76% yield as a mixture of *cis* and *trans* diastereomers and, according to the ^{1}H NMR spectrum, does not contain oxidation product impurities. This method is the first efficient procedure for preparing 4-aryl-ubstituted Guareschi imides and one of the first examples of the use of azolide **2** as an active methylene compound serving as an alternative to ethyl cyanoacetate. Work on the optimization of the method and clarification of its scope is currently underway.

*To whom correspondence should be addressed, e-mail: Victor_Dotsenko@bigmir.net.

[1]G.S. Petrov Research Institute of Plastics, Perovsky proezd 35, Moscow 111024, Russia.
[2]ChemEx Laboratory, Volodimir Dahl East Ukrainian National University, 20a, build. 7 Molodezhnyi Qr., Lugansk 91034, Ukraine.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 1108–1110, July, 2011. Original article submitted March 2, 2011.



1, **3** Ar = 2-ClC_6H_4

The IR spectra were obtained on an IKS-29 spectrometer in nujol mulls. The ^1H and ^{13}C NMR spectra were taken on a Bruker DRX-500 spectrometer at 500 and 125 MHz, respectively, in DMSO-d_6 with TMS as internal standard. The elemental analysis was carried out on a Perkin-Elmer CHN analyzer.

Triethylammonium 4-(2-Chlorophenyl)-3,5-dicyano-6-oxo-1,4,5,6-tetrahydropyridin-2-olate (1). Triethylamine dried over KOH (1.2 ml, 8.6 mmol) was added to a mixture of (*E*)-3-(2-chlorophenyl)-2-cyanoacrylamide **3** (1.20 g, 5.8 mmol) and cyanoacetylpyrazole **2** (1.10 g, 6.7 mmol) in warm acetone (15 ml). The flask with the reaction mixture was left at 10–15°C for 72–120 h. The white crystalline precipitate was filtered off and washed with cold acetone and ether to give 1.64 g (76%) pure salt **1**; mp >250°C; R_f 0.69 (acetone–hexane, 1:1). *Attention!* This compound causes sneezing. IR spectrum, ν, cm^{-1}: 3170 (NH), 2255 (unconj. C≡N), 2175 (C≡N), 1695 (C=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.16 (9H, t, $^3J = 7.1$, $3CH_3CH_2$); 3.05 (6H, q, $^3J = 7.1$, $3CH_3CH_2$); 4.19–4.79 (2H, m, superposition of signals of diastereomeric H-4 and H-5); 7.27–7.50 (4H, m, H Ar); 9.71 (1H, br. s, NH). The signals of the NH^+ proton are not seen due to deuterium exchange. ^{13}C NMR spectrum, δ, ppm: 9.34, 37.30, 41.78, 46.31, 128.07, 128.17, 129.10, 129.32, 129.75, 129.97, 133.13, 133.70, 138.47, 140.50, 164.32, 164.51. Found, %: C 61.14; H 6.24; N 14.90. $C_{19}H_{23}ClN_4O_2$. Calculated, %: C 60.88; H, 6.18; N 14.95.

REFERENCES

1. S. A. El Batran, A. E. N. Osman, M. M. Ismail, and A. M. El Sayed, *Inflammopharmacology,* **14**, 62 (2006) and references cited therein.
2. N. S. Zefirov and S. V. Rogozina, *Usp. Khim.*, **42**, 423 (1973).
3. R. Jeyaraman and R. S. Avilliva, *Chem. Rev.*, **81**, 149 (1981).
4. P. Jimonet, Y. Ribeill, G. A. Bohme, A. Boireau, M. Chevée, D. Damour, A. Doble, A. Genevois-Borella, F. Herman, A. Imperato, S. Le Guern, F. Manfrée, J. Pratt, J. C. R. Randle, J.-M. Stutzmann, and S. Mignani, *J. Med. Chem.*, **43**, 2371 (2000).
5. A. M. Badger, D. A. Schwartz, D. H. Picker, J. W. Dorman, F. C. Bradley, E. N. Cheeseman, M. J. DiMartino, N. Hanna, and C. K. Mirabelli, *J. Med. Chem.*, **33**, 2963 (1990).
6. S. M. McElvain and D. H. Clemens, *J. Am. Chem. Soc.*, **80**, 3915 (1958).
7. I. Guareschi, *Chem. Zentralbl.*, **69**, Pt 2, 544 (1898).
8. I. Guareschi, *Chem. Zentralbl.*, **72**, Pt 1, 579 (1901).
9. I. Guareschi, *Gazz. Chim. Ital.*, **49**(1), 124 (1919).
10. I. Guareschi and E. Grande, *Chem. Zentralbl.*, **70**, Pt 2, 439 (1899).
11. G. J. Handley, E. R. Nelson, and T. C. Somers, *Austr. J. Chem.*, **13**, 129 (1960) and references cited therein.
12. R. W. Holder, J. P. Daub, W. E. Baker, R. H. Gilbert, III, and N. A. Graf, *J. Org. Chem*, **47**, 1445 (1982).
13. A. A. Liebman and F. E. Digangi, *J. Pharm. Sci.*, **52**, 395 (1963).
14. B. Nguyen, K. Chernous, D. Endlar, B. Odell, M. Piacenti, J. M. Brown, A. S. Dorofeev, and A. V. Burasov, *Angew. Chem. Ind. Ed.*, **46**, 7655 (2007).

15. I. Guareschi, *Atti R. Accad. Sci. Torino*, **32**, 399 (1897).
16. J. L. Soto, A. Lorente, and L. Fuentes, *An. Quim.*, **74**, 648 (1978).
17. J. N. E. Day and J. F. Thorpe, *J. Chem. Soc. (C)*, **117**, 1465 (1920).
18. J. S. A. Brunskill, *J. Chem. Soc. (C)*, 960 (198) and references cited therein.
19. N. M. Fathy and G. H. Elgemeie, *J. Chem. Eng. Data*, **33**, 218 (1988).
20. N. Palit, *J. Indian Chem. Soc.*, **14**, 219 (1937).
21. L. Wu, C. Yang, L. Yang, and L. Yang, *Heterocycles*, **78**, 977 (2009).
22. W. Ried and A. Meyer, *Chem. Ber.*, **90**, 2841 (1957).
23. N. Yu. Gorobets, B. H. Yousefi, F. Belaj, and C. O. Kappe, *Tetrahedron*, **60**, 8633 (2004).