Available online at www.sciencedirect.com

ScienceDirect

Mendeleev Commun., 2019, **29**, 232–233

Mendeleev Communications

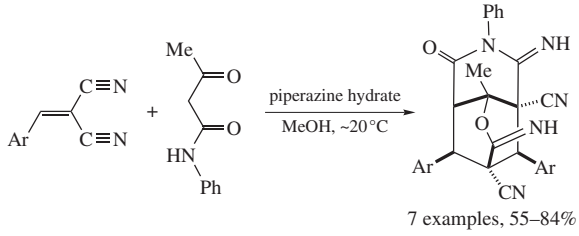
Efficient synthesis of new tricyclic pyrano[3,2-*c*]pyridine derivatives

Ibrahim G. Mamedov,*[a] Victor N. Khrustalev,[b,c] Pavel V. Dorovatovskii,[c] Farid N. Naghiev[a] and Abel M. Maharramov[a]

[a] *Department of Chemistry, Baku State University, AZ1148 Baku, Azerbaijan. E-mail: bsu.nmrlab@mail.ru*
[b] *Peoples Friendship University of Russia (RUDN University), 117198 Moscow, Russian Federation*
[c] *National Research Center 'Kurchatov Institute', 123098 Moscow, Russian Federation*

DOI: 10.1016/j.mencom.2019.03.040

Reaction between arylidenemalononitriles and acetoacetanilide in the presence of piperazine hydrate in methanol at room temperature affords new tricyclic pyrano[3,2-*c*]pyridine derivatives of (*rac*-1*S,2*R**,3*R**,7*R**,8*R**,11*R**)-2,11-diaryl-4,10-diimino-8-methyl-5-phenyl-6-oxo-9-oxa-5-azatricyclo-[5.3.1.0^{3,8}]undecane-1,3-dicarbonitrile family in yields of 55–84%. The molecular structures of the products were confirmed by X-ray crystallography and NMR spectroscopy.**



Polyfunctional heterocyclic systems are often accessed *via* the Michael addition of active methylene compounds at the Knoevenagel nitriles.[1–5] Many such compounds exhibit biological activities including anticancer, antimicrobial, antiulcer, antipyretic, and anti-inflammatory ones.[6–8]

The use of acetoacetanilides, aromatic aldehydes, malononitrile as substrates in such protocols affords substituted 4*H*-pyrans and pyridines. Starting from equimolar amounts of the reactants with various bases in ethanol, bicyclic pyranopyridines were synthesized.[9–12] Herein, we found that when the amount of arylidenemalononitriles **1a**–**g** was doubled in respect to acetoacetanilide **2** (the reaction was processed in the presence of piperazine hydrate in methanol at room temperature), tricyclic pyrano[3,2-*c*]pyridine derivatives **3a**–**g** were obtained (Scheme 1).†

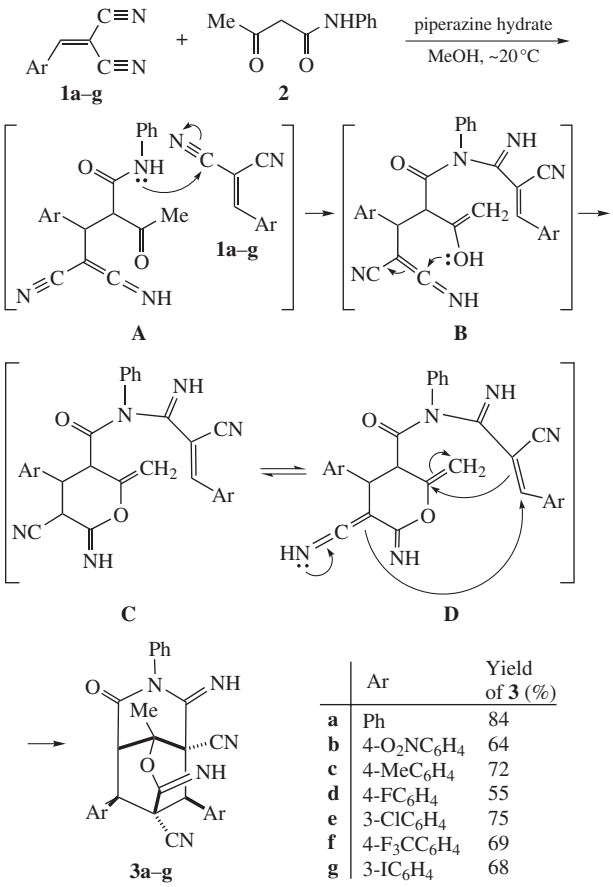
According to the tentative mechanism of the transformation (see Scheme 1), the second molecule of arylidenemalononitrile reacts with the primary Knoevenagel adduct **A** to furnish intermediate **B**. The subsequent intramolecular enolization, electron redistribution and cyclization lead to species **C** and/or **D**. At the final step, electron and proton redistribution affords tricyclic compound **3**.

† *General procedure for the synthesis of compounds* **3a**–**g**. To a stirred mixture of benzylidenemalononitrile **1a**–**g** (8 mmol), acetoacetanilide **2** (0.72 g, 4 mmol) and methanol (20 ml), piperazine hydrate (0.22 g, 7 mol%) was added, and the mixture was left overnight (TLC control). The solvent was removed to leave a solid material which was washed on a paper filter 4 times with an ethanol–water mixture, and finally dried in air.

4,10-Diimino-8-methyl-2,5,11-triphenyl-6-oxo-9-oxa-5-azatricyclo-[5.3.1.0^{3,8}]undecane-1,3-dicarbonitrile **3a**, white powder, yield 84%, mp 276 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.91 (s, 3H, Me-19), 3.95 (d, 1H, C^{11}H, $^3J_{H,H}$ 3.0 Hz), 4.49 (d, 1H, C^{7}H, $^3J_{H,H}$ 3.0 Hz), 4.94 (s, 1H, C^{2}H), 7.37–7.64 (m, 15H, 3Ar), 7.88 (s, 1H, N^{13}H), 9.20 (s, 1H, N^{18}H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 22.19 (19-Me), 48.15 (C^3), 49.29 (C^{11}H), 50.85 (C^{7}H), 51.30 (C^{2}H), 55.58 (C^1), 76.35 (C^8), 115.13 (C^{16}N), 115.79 (C^{14}N), 128.88 (CH$_{arom}$), 129.08 (CH$_{arom}$), 129.32 (CH$_{arom}$), 129.53 (CH$_{arom}$), 129.64 (CH$_{arom}$), 129.71 (CH$_{arom}$), 129.85 (CH$_{arom}$), 130.29 (CH$_{arom}$), 130.66 (CH$_{arom}$), 133.76 (C$_{arom}$), 136.01 (C$_{arom}$), 137.83 (C$_{arom}$), 154.63 (N=C^{10}), 155.59 (N=C^4), 167.62 (C^{12}=O).

For characteristics of compounds **3b**–**g**, see Online Supplementary Materials.

^{1}H NMR spectra of obtained compounds **3a**–**g** contain three different signals for CH protons in the range 3.8–5.1 ppm. The ^{13}C NMR spectra exhibit one signal for the methyl group, three different CH signals and three different quaternary aliphatic carbon signals at the relevant range. The signals are not doubled, which is the evidence of formation of the single diastereomer of the product.



	Ar	Yield of **3** (%)
a	Ph	84
b	4-$O_2NC_6H_4$	64
c	4-MeC_6H_4	72
d	4-FC_6H_4	55
e	3-ClC_6H_4	75
f	4-$F_3CC_6H_4$	69
g	3-IC_6H_4	68

Scheme 1

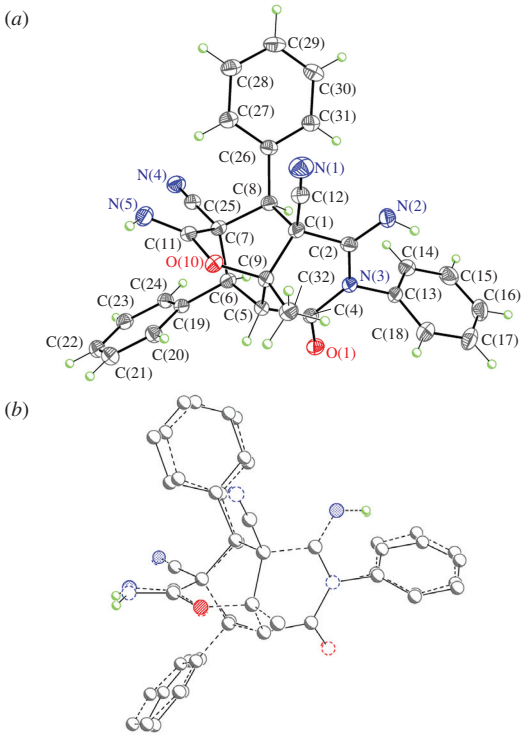


Figure 1 (*a*) Molecular structure and (*b*) a superposition of the two crystallographically independent molecules of compound **3a**.

The structure and configuration of compound **3a** were unambiguously established by X-ray diffraction study [Figure 1(*a*)]. It crystallizes in the triclinic space group $P\bar{1}$ with two crystallographically independent molecules in the unit cell, which attain very close geometries [Figure 1(*b*)].‡

Compound **3a** represents a heterocyclic complex containing three six-membered rings – one piperidine and two tetrahydropyran ones (see Figure 1). The piperidine ring adopts a slightly distorted half-chair conformation, whereas the both tetrahydropyran rings have boat conformations. X-ray study of crystal **3a** allowed us to derive relative configuration of six asymmetric centers at C(1), C(5), C(6), C(7), C(8) and C(9) and therefore to assign configuration of all the series **3a–g** as *rac*-1*S**,2*R**,3*R**,7*R**,8*R**,11*R** (atom numbering in the crystal study was different from systematic). In the crystal, molecules of **3a** form H-bonded dimers *via* the two intermolecular hydrogen bonds N(5)–H···N(9) [N···N 3.252(3), H···N 2.51 Å, ∠N–H···N 139°] and N(9)–H···O(10) [N···O 3.019(3), H···O 2.56 Å, ∠N–H···O 112°] (Figure 2). The dimers are packed into stacks along the crystallographic *b* axis. The crystal of **3a** is racemic and consist of enantiomeric pairs.

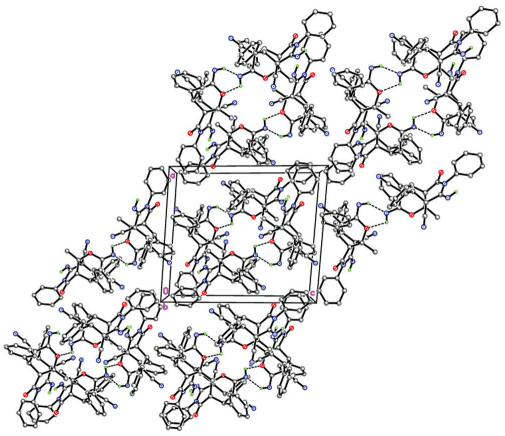


Figure 2 Crystal structure of **3a** demonstrating the H-bonded dimers.

In summary, we successfully synthesized a new family of 2,11-diaryl-4,10-diimino-8-methyl-5-phenyl-6-oxo-9-oxa-5-aza-tricyclo[5.3.1.$0^{3,8}$]undecane-1,3-dicarbonitriles *via* the reaction of available arylienemalononitriles with the acetoacetanilide at room temperature in the presence of piperazine hydrate in methanol. The procedure is simple and looks promising for efficient access to functionalized cyclic pyranopyridines with valuable properties.

This work was supported by the RUDN University Program '5-100'. Synchrotron radiation-based single-crystal X-ray diffraction measurements were performed at the unique scientific facility Kurchatov Synchrotron Radiation Source supported by the Ministry of Education and Science of the Russian Federation (project no. RFMEFI61917X0007).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.03.040.

References

1 J. M. Khurana and A. Chaudhary, *Green Chem. Lett. Rev.*, 2012, **5**, 633.
2 C. Allais, J. M. Grassot, J. Rodriguez and T. Constantieux, *Chem. Rev.*, 2014, **114**, 10829.
3 J. A. Bull, J. J. Mousseau, G. Pelletier and A. B. Charette, *Chem. Rev.*, 2012, **112**, 2642.
4 M. N. Elinson, F. V. Ryzhkov, A. N. Vereshchagin, A. D. Korshunov, R. A. Novikov and M. P. Egorov, *Mendeleev Commun.*, 2017, **27**, 559.
5 M. N. Elinson, A. N. Vereshchagin, Yu. E. Anisina, A. S. Goloveshkin, I. E. Ushakov and M. P. Egorov, *Mendeleev Commun.*, 2018, **28**, 372.
6 A. H. Abadi, D. A. Abouel-Ella, J. Lehmann, H. N. Tinsley, B. D. Gary, G. A. Piazza and M. A. O. Abdel-Fattah, *Eur. J. Med. Chem.*, 2010, **45**, 90.
7 H. Xiao, P. Li, D. Guo, J. Hu, Y. Chai and W. He, *Med. Chem. Res.*, 2014, **23**, 1941.
8 O. V. Bykhovskaya, I. M. Aladzheva, M. V. Makarov, E. Yu. Rybalkina, Z. S. Klemenkova and V. K. Brel, *Russ. Chem. Bull., Int. Ed.*, 2017, **66**, 104 (*Izv. Akad. Nauk, Ser. Khim.*, 2017, 104).
9 R. Pagadala, S. Maddila and S. B. Jonnalagadda, *Org. Prep. Proced. Int.*, 2014, **46**, 261.
10 R. A. Azzam and R. M. Mohareb, *Chem. Pharm. Bull.*, 2015, **63**, 1055.
11 S. Maddila, R. Padala, S. Rana, S. Kankala and S. B. Jonnalagadda, *Res. Chem. Intermed.*, 2015, **41**, 8269.
12 X. Xin, Y. Wang, S. Kumar, X. Liu, Y. Lin and D. Dong, *Org. Biomol. Chem.*, 2010, **8**, 3078.
13 T. G. G. Battye, L. Kontogiannis, O. Johnson, H. R. Powell and A. G. W. Leslie, *Acta Crystallogr.*, 2011, **D67**, 271.
14 P. R. Evans, *Acta Crystallogr.*, 2006, **D62**, 72.
15 G. M. Sheldrick, *Acta Crystallogr.*, 2015, **C71**, 3.

Received: 10th September 2018; Com. 18/5685

‡ Single-crystal X-ray diffraction data for **3a** were collected on the 'Belok' beamline of the Kurchatov Synchrotron Radiation Source (National Research Center 'Kurchatov Institute', Moscow, Russian Federation) using a Rayonix SX165 CCD detector at λ = 0.81182 Å. A total of 720 images for two different orientations of the crystal was collected using an oscillation range of 1.0° and φ scan mode. The data were indexed and integrated using the utility iMOSFLM from the CCP4 program suite[13] and then scaled and corrected for absorption using the Scala program.[14] All calculations were carried out using the SHELXTL program suite.[15]

Crystal data for **3a**: $C_{30}H_{23}N_5O_2$ (M = 485.53), triclinic, space group $P\bar{1}$, at 100 K: a = 12.854 (3), b = 13.615(3) and c = 14.632(3) Å, β = = 84.59(3)°, V = 2492.6(10) Å^3, Z = 4, d_{calc} = 1.294 g cm^{-3}, μ = 0.111 mm^{-1}, F(000) = 1016, 42719 reflections were measured and 10194 independent reflections (R_{int} = 0.0071) were used in a further refinement. The refinement converged to wR_2 = 0.163 and GOF = 1.037 for all independent reflections [R_1 = 0.0061 was calculated against F for 7670 observed reflections with $I > 2\sigma(I)$]. The hydrogen atom positions were fixed geometrically at calculated distances and allowed them to ride on the parent atoms.

CCDC 1854454 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.