FULL PAPER

N,*N*′-Bis(arylmethylidene)arylmethanediamines: Suitable Precursors for the Synthesis of 1-Pyrroline Derivatives

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A simple and appropriate procedure for the synthesis of 4,5-dihydro-5-hydroxy-3*H*-pyrrole-3,3-dicarbonitrile derivatives is reported. The advantages of this method are one-pot conditions, high yield of products, short reaction times, and no need of metal catalyst. The structures are confirmed spectroscopically (IR, ^{1}H- and ^{13}C-NMR, and EI-MS) and by elemental analyses. A plausible mechanism for this reaction is proposed (*Scheme 2*).

Keywords: *N*-Containing heterocycles, 1-Pyrroline, Phenacylbromide, Multicomponent reaction, Arylmethanediamines, *N*,*N*′-bis(arylmethylidene)-

Introduction

Five-membered, *N*-containing heterocycles such as pyrrole, pyrroline, and pyrrolidine are important frameworks of various natural products and have attracted much attention due to their biological activities [1]. These properties include antibacterial [2], antifungal [3], antioxidant [4], anti-HIV, and antitumor activities [5][6]. There exist three isomeric structures for dihydro derivatives of pyrrole, among them, 1-pyrrolines are the most important. These compounds are key intermediates and can be widely used in organic synthesis. They are present in important biologically active compounds such as hemes, chlorophylls [7], and alkaloids [8]. 1-Pyrrolines also occur in many natural products such as eudistomins, pyracrimycin A, and myosmine [9] (*Fig.*).

Due to the importance of these heterocycles, several methods for the synthesis of 1-pyrrolines have been reported. For instance, [3 + 2] cycloaddition of isocyanoacetates with electron-deficient olefins [10], ring expansion of *N*-vinylaziridine using dipolarophiles [9], and reaction of γ-bromonitrile with aryl *Grignard* reagents [11]. Most of these methods have some disadvantages, like multistep synthesis, using toxic organic solvent, and moderate yield of products. *N*,*N*′-Bis(arylmethylidene)-arylmethanediamines are suitable precursors for the synthesis of *N*-containing heterocycles [12][13]. They can be obtained easily from the reaction of aromatic aldehydes and NH_3 solution or hexamethyldisilazane (HMDS) [14].

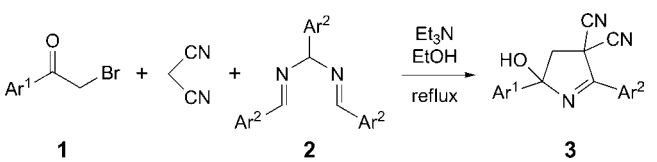
Previously, our research group has reported divers multicomponent reactions (MCRs) for generating some aza-cyclic compounds using *N*,*N*′-bis(phenylmethylidene)-phenylmethanediamines [15][16]. In continuation and considering the importance of the 1-pyrroline scaffold, we describe in this article a one-pot, three-component reaction of phenacylbromide derivatives **1**, malononitrile, and *N*,*N*′-bis(arylmethylidene)-arylmethanediamines **2** in the presence of Et_3N as catalyst in EtOH to afford 4,5-dihydro-5-hydroxy-3*H*-pyrrole-3,3-dicarbonitrile derivatives **3** in high yields (*Scheme 1*).

Results and Discussion

Initially, a mixture of phenacylbromide (**1a**, Ar^1 = Ph, 1 mmol) and malononitrile (1 mmol) in EtOH in the presence of Et_3N (1 mmol) was stirred at room temperature for 10 min. Then, *N*,*N*′-bis(phenylmethylidene)phenylmethanediamine (**2a**; Ar^2 = Ph, 1 mmol) was added to

Figure. Natural products containing 2-substituted pyrrolines.

Scheme 1. One-pot synthesis of 1-pyrroline derivatives **3**.



 DOI: 10.1002/hlca.201500251

the mixture mentioned above, and the resulting mixture was refluxed for 1 h to afford compound **3a** in high yield.

The isolated product was characterized by IR, ^{1}H- and ^{13}C-NMR, and mass spectroscopic analyses. The mass spectrum of **3a** displayed a molecular-ion peak at *m*/*z* 287. In the IR spectrum, three stretching frequencies at 3427, 2251, and 1617 are related to OH, C≡N, and C=N groups, respectively. The ^{1}H-NMR spectrum showed one *AB* system arising from the CH_2 group, one *singlet* at 6.17 ppm due to the OH group, and characteristic signals with appropriate chemical shifts and coupling constants for 10 H-atoms of the aromatic region. The ^{1}H-decoupled ^{13}C-NMR spectrum of **3a** exhibited 14 distinct signals in agreement with the proposed structure.

To study the scope of this reaction, different substituted phenacylbromides and some *N*,*N*′-bis(arylmethylidene)-arylmethanediamines were applied under the same reaction condition (*Scheme 1*). As shown in the *Table*, the results are acceptable in all cases.

The proposed mechanism for this reaction is presented in *Scheme 2*. It is plausible that the initial event is a nucleophilic attack of the anion of malononitrile to phenacylbromide (**1a**) [17][18]. Under basic conditions, the resulting anionic intermediate **A** attacks on compound **2a** to give **B**. Intramolecular cyclization of **B** generates **C** and subsequent loss of **D** leads to the formation of the product **3a**.

It is noteworthy, when compound **2** was replaced by *N*-benzylidene-1-phenylmethanamine (**D**) under the same conditions, no product **3** was formed. The exact reason for this is not clear, but we suppose that the presence of the second imine in *N*,*N*′-bis(phenylmethylidene)phenylmethanediamine causes the imine bond more reactive compared with a compound having only one imine bond in its structure.

In conclusion, we have developed a one-pot, three-component reaction of phenacylbromide derivatives, malononitrile, and *N*,*N*′-bis(arylmethylidene)-arylmethanediamines, for the synthesis of 1-pyrrolines. These products have potential applications in medicinal chemistry and in organic synthesis. The present method has some benefits such as mild reaction condition, using available starting materials, short reaction times, and high yield of products.

We gratefully acknowledge the financial support received for this research from *Tarbiat Modares University*, Iran.

Table. Synthesis of 4,5-dihydro-5-hydroxy-3*H*-pyrrole-3,3-dicarbonitrile derivatives **3** (*Scheme 1*)

Entry	Ar^1	Ar^2	Time [min]	Product	Yield [%][a])
1	Ph	Ph	60	**3a**	90
2	4-MeO–C_6H_4	Ph	90	**3b**	70
3	4-Cl–C_6H_4	Ph	70	**3c**	85
4	4-Br–C_6H_4	Ph	75	**3d**	82
5	Ph	4-Me–C_6H_4	60	**3e**	87
6	Ph	4-MeO–C_6H_4	60	**3f**	82

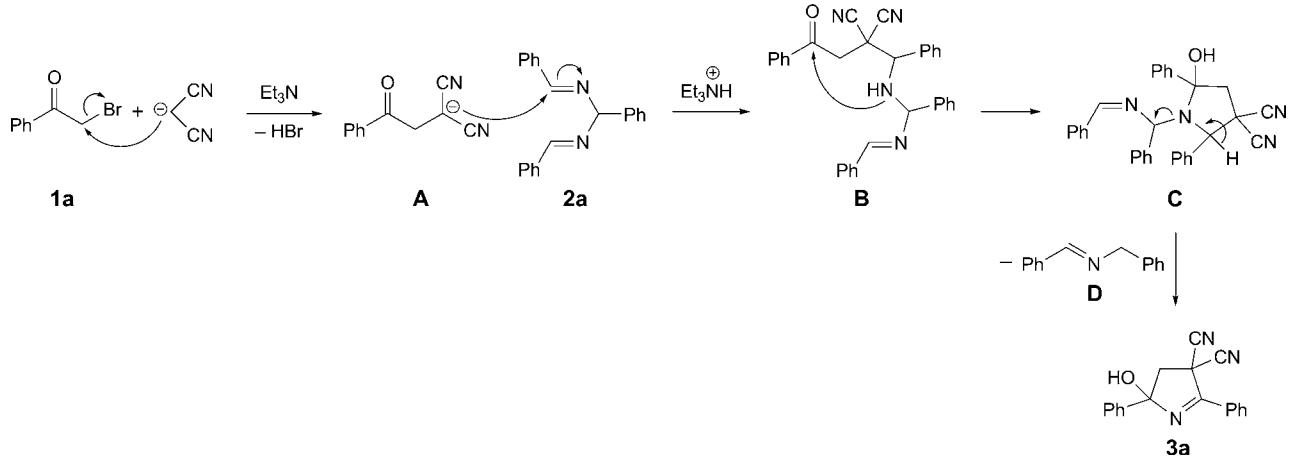
[a]) Yield of isolated product.

Experimental Part

General

All starting materials were obtained from *Merck* (Germany) and *Fluka* (Switzerland) and were used without further purification. *N*,*N*′-Bis(arylmethylidene)-arylmethanediamines were prepared according to published procedures [12]. M.p.: *Electrothermal 9100* apparatus. IR Spectra: *Shimadzu IR-460* spectrometer in KBr; $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR spectra: *Bruker DRX 300-AVANCE* FT-NMR instrument, at 300 and 75 MHz,

Scheme 2. Proposed mechanism of this reaction.



resp., in (D_6)DMSO if not otherwise stated; δ in ppm rel. to Me_4Si as internal standard, J in Hz. MS: *FINNIGAN-MAT 8430* mass spectrometer operating at an ionization potential of 70 eV; in m/z (rel. %). Elemental analyses for C, H, and N: *Heraeus CHN–O–Rapid* analyzer.

Syntheses of Compounds **3** *(exemplified for* **3a***)*

A soln. of phenacylbromide (**1a**; 1 mmol), malononitrile (1 mmol), and Et_3N (1 mmol) in EtOH (5 ml) was stirred at r.t. for 10 min. Then, *N*,*N*′-bis(phenylmethylidene)phenylmethanediamine (**2a**; 1 mmol) was added to the mixture at reflux temp. After completion of the reaction (monitored by TLC), **3a** was obtained after purification by column chromatography using hexane/AcOEt 7:1.

4,5-Dihydro-5-hydroxy-2,5-diphenyl-3*H*-pyrrole-3,3-dicarbonitrile (**3a**). Yield: 0.26 g (90%). Cream powder. M.p. 122 °C. IR: 3427 (OH), 2251 (CN), 1617 (C=N), 1492 and 1445 (Ar). ^{1}H-NMR: 4.20, 4.35 (*AB*, ^2J = 17.2, 2 H); 6.17 (*s*, 1 H); 7.46 – 7.48 (*m*, 5 H); 7.52 – 7.62 (*m*, 3 H); 7.96 (*d*, ^3J = 7.7, 2 H). ^{13}C-NMR: 40.6; 46.8; 81.4; 114.2; 115.7; 127.1; 128.2; 128.8; 128.9; 129.1; 131.8; 132.1; 135.9; 170.8. EI-MS: 287 (M^+, 2), 271 (34), 222 (40), 193 (100), 165 (21), 89 (34), 77 (23). Anal. calc. for $C_{18}H_{13}N_3O$ (287.32): C 75.25, H 4.56, N 14.62; found: C 77.30, H 4.52, N 14.57.

4,5-Dihydro-5-hydroxy-5-(4-methoxyphenyl)-2-phenyl-3*H*-pyrrole-3,3-dicarbonitrile (**3b**). Yield: 0.27 g (87%). Yellow powder. M.p. 138 – 140 °C. IR: 3427 (OH), 2248 (CN), 1602 (C=N), 1511 and 1449 (Ar). ^{1}H-NMR: 3.83 (*s*, 3 H); 4.14, 4.35 (*AB*, ^2J = 17.1, 2 H); 6.09 (*s*, 1 H); 7.08 (*d*, ^3J = 8.7, 2 H); 7.42 – 7.46 (*m*, 5 H); 7.90 (*d*, ^3J = 8.7, 2 H). ^{13}C-NMR: 40.6; 46.7; 55.5; 81.2; 114.2; 114.3; 115.8; 124.4; 127.1; 128.8; 129.0; 130.1; 136.2; 162.3; 169.9. EI-MS: 317 (M^+, 1), 301 (73), 252 (11), 223 (100), 208 (100), 180 (17), 89 (13). Anal. calc. for $C_{19}H_{15}N_3O_2$ (317.35): C 71.91, H 4.76, N 13.24; found: C 71.85, H 4.70, N 13.31.

5-(4-Chlorophenyl)-4,5-dihydro-5-hydroxy-2-phenyl-3*H*-pyrrole-3,3-dicarbonitrile (**3c**). Yield: 0.33 g (90%). Cream powder. M.p. 156 – 158 °C. IR: 3441 (OH), 2250 (CN), 1621 (C=N), 1492 and 1450 (Ar). ^{1}H-NMR: 4.21, 4.35 (*AB*, ^2J = 17.4, 2 H); 6.17 (*s*, 1 H); 7.43 – 7.48 (*m*, 5 H); 7.63 (*d*, ^3J = 8.6, 2 H); 7.96 (*d*, ^3J = 8.5, 2 H). ^{13}C-NMR: 40.7; 46.8; 81.4; 114.1; 115.6; 127.2; 128.8; 129.0; 129.2; 130.0; 130.6; 135.8; 136.9; 169.9. EI-MS: 322 (M^+, 1), 307 (16), 305 (57), 250 (21), 227 (100), 192 (40), 89 (67). Anal. calc. for $C_{18}H_{12}ClN_3O$ (321.76): C 67.19, H 3.76, N 13.06; found: C 67.15, H 3.84, N 13.11.

5-(4-Bromophenyl)-4,5-dihydro-5-hydroxy-2-phenyl-3*H*-pyrrole-3,3-dicarbonitrile (**3d**). Yield: 0.27 g (85%). Cream powder. M.p. 160 – 162 °C. IR: 3440 (OH), 2238 (CN), 1613 (C=N), 1448 and 1488 (Ar). ^{1}H-NMR: 4.20, 4.33 (*AB*, ^2J = 17.3, 2 H); 6.16 (*s*, 1 H), 7.42 – 7.47 (*m*, 5 H); 7.76 (*d*, ^3J = 8.5, 2 H); 7.88 (*d*, ^3J = 8.5, 2 H). ^{13}C-NMR: 40.7; 46.8; 81.5; 114.1; 115.7; 125.9; 127.2; 128.8; 129.2; 130.2; 130.9; 131.9; 135.8; 170.1. EI-MS: 351 (30), 349 (30), 273 (100), 271 (100), 192 (36), 165 (37), 89 (46). Anal. calc. for $C_{18}H_{12}BrN_3O$ (366.22): C 59.04, H 3.30, N 11.47; found: C 71.10, H 4.15, N 8.60.

4,5-Dihydro-5-hydroxy-2-(4-methylphenyl)-5-phenyl-3*H*-pyrrole-3,3-dicarbonitrile (**3e**). Yield: 0.27 g (89%). White powder. M.p. 119 °C. IR: 3438 (OH), 2245 (CN), 1629 (C=N), 1574, 1508 and 1446 (Ar). ^{1}H-NMR: 2.33 (*s*, 3 H); 4.18, 4.32 (*AB*, ^2J = 17.2, 2 H); 6.11 (*s*, 1 H); 7.78 (*d*, ^3J = 8.1, 2 H); 7.33 (*d*, ^3J = 8.1, 2 H); 7.51 – 7.61 (*m*, 3 H); 7.95 (*d*, ^3J = 6.9, 2 H). ^{13}C-NMR: 20.8; 40.7; 46.7; 81.3; 114.3; 115.8; 127.1; 128.2; 128.8; 129.3; 131.7; 132.1; 132.9; 138.4; 170.6. EI-MS: 301 (M^+, 1), 285 (44), 223 (88), 207 (100), 165 (11), 103 (25), 77 (15). Anal. calc. for $C_{19}H_{15}N_3O$ (301.34): C 75.73, H 5.02, N 13.94; found: C 75.80, H 5.07, N 14.02.

4,5-Dihydro-5-hydroxy-2-(4-methoxyphenyl)-5-phenyl-3*H*-pyrrole-3,3-dicarbonitrile (**3f**). Yield: 0.25 g (80%). Yellow powder. M.p. 115 – 116 °C. IR: 3442 (OH), 2246 (CN), 1626 (C=N), 1573, 1508 and 1446 (Ar). ^{1}H-NMR: 3.78 (*s*, 3 H); 4.18, 4.31 (*AB*, ^2J = 17.3, 2 H); 6.11 (*s*, 1 H); 7.03 (*d*, ^3J = 8.7, 2 H); 7.37 (*d*, ^3J = 8.7, 2 H); 7.50 – 7.61 (*m*, 3 H); 7.95 (*d*, ^3J = 6.9, 2 H). ^{13}C-NMR: 40.8; 46.6; 55.1; 81.2; 114.1; 114.3; 115.8; 127.7; 128.2; 128.5; 128.9; 131.8; 132.1; 159.7; 170.5. EI-MS: 301 (48), 223 (100), 208 (64), 184 (40), 120 (28), 91 (43), 77 (44). Anal. calc. for $C_{19}H_{15}N_3O_2$ (317.34): C 71.91, H 4.76, N 13.24; found: C 71.86, H 4.80, N 13.30.

REFERENCES

[1] F. Bellina, R. Rossi, *Tetrahedron* **2006**, *62*, 7213.

[2] M. V. Raimondi, S. Cascioferro, D. Schillaci, S. Petruso, *Eur. J. Med. Chem.* **2006**, *41*, 1439; A. Al-Mourabit, M. A. Zancanella, S. Tilvi, D. Romo, *Nat. Prod. Rep*. **2011**, *28*, 1229.

[3] M. Del Poeta, W. A. Schell, C. C. Dykstra, S. Jones, R. R. Tidwell, A. Czarny, M. Bajic, M. Bajic, A. Kumar, D. Boykin, J. R. Perfect, *Antimicrob. Agents Chemother.* **1998**, *42*, 2495; M.-Z. Wang, H. Xu, T.-W. Liu, Q. Feng, S.-J. Yu, S.-H. Wang, Z.-M. Li, *Eur. J. Med. Chem*. **2011**, *46*, 1463.

[4] J. Lehuédé, B. Fauconneau, L. Barrier, M. Ourakow, A. Piriou, J.-M. Vierfond, *Eur. J. Med. Chem.* **1999**, *34*, 991; D. Wang, X. Hu, G. Zhao, *Int. J. Food Sci. Technol*. **2008**, *43*, 1880.

[5] G. A. Pinna, G. Loriga, G. Murineddu, G. Grella, M. Mura, L. Vargiu, C. Murgioni, P. La Colla, *Chem. Pharm. Bull.* **2001**, *49*, 1406; C. Boonlarppradab, C. A. Kauffman, P. R. Jensen, W. Fenical, *Org. Lett*. **2008**, *10*, 5505.

[6] T. Fucuda, F. Ishibashi, M. Iwao, *Heterocycles* **2011**, *83*, 491.

[7] T. A. Dineen, K. Chen, A. C. Cheng, K. Derakhchan, O. Epstein, J. Esmay, D. Hickman, C. E. Kreiman, I. E. Marx, R. C. Wahl, P. H. Wen, M. M. Weiss, D. A. Whittington, S. Wood, R. T. Fremeau Jr, R. D. White, V. F. Patel, *J. Med. Chem.* **2014**, *57*, 9811.

[8] N. Laohakunjit, A. Noomhorm, *Flavour Fragrance J.* **2004**, *19*, 251; A. Pluotno, S. Varmeli, *Tetrahedron* **2005**, *61*, 575.

[9] S. S. More, T. Krishna Mohan, Y. Sateesh Kumar, U. K. Syam Kumar, N. B. Patel, *Beilstein J. Org. Chem.* **2011**, *7*, 831.

[10] S. Padilla, J. Adrio, J. C. Carretero, *J. Org. Chem.* **2012**, *77*, 4161.

[11] P. J. Demoen, P. A. Janssen, *J. Am. Chem. Soc.* **1959**, *81*, 6281.

[12] O. V. Ershov, A. V. Eremkin, Y. S. Kayukov, A. N. Lyshchikov, O. E. Nasakin, V. A. Tafeenko, *Russian J. Org. Chem.* **2008**, *44*, 570.

[13] A. B. Zolotoi, A. N. Lyshchikov, P. M. Lukin, A. I. Prokhorov, O. E. Nasakin, A. Kh. Bulai, L. O. Atovmyan, *Dokl. Acad. Nauk SSSR* **1990**, *313*, 110.
[14] P. Y. Reddy, M. Shimizu, K. Higashi, T. Shimizu, T. Toru, *Arkivoc* **2001**, *(viii)*, 111.
[15] A. Alizadeh, J. Mokhtari, M. Ahmadi, *Tetrahedron* **2012**, *68*, 319.
[16] A. Alizadeh, J. Mokhtari, L.-G. Zhu, *C. R. Chim.* **2013**, *16*, 863.
[17] S. M. Al-Mousawi, M. S. Moustafa, H. Meier, H. Kolshorn, M. H. Elnagdi, *Molecules* **2009**, *14*, 798.
[18] F. M. Abdelrazek, A. W. Erian, K. M. H. Hilmy, *Synthesis* **1986**, *74*.

Received October 3, 2015
Accepted January 22, 2016

