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One-pot synthesis of 2-(dicyanomethylene)-1,2-dihydropyridine derivatives

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ABSTRACT

The synthesis of 2-(dicyanomethylene)-1,2-dihydropyridine derivatives from the reactions of arylmethylidene derivatives of malononitrile dimers with 1,3-dicarbonyl compounds is described.

1,3-Dicarbonyl compounds are important chemical substrates for the synthesis of various medicines that contain an azaheterocyclic fragment. Examples include vitamin B6, antipyrine, aminopyrine, aminoglutethimide, and various analgesics, antibacterial, and antimalarial medications. In addition, 1,3-dicarbonyl compounds are important for the synthesis of new biologically active compounds, such as functionally substituted pyridin-2-ones, for example, **1** and their hydrogenated analogs,[1a–e] for example, inhibitors of Rho-associated kinase,[1a] and the glycine site on the NMDA receptor, and for AMPA antagonist activity,[1b] inhibition of PARP activity,[1c] cytotoxic activity,[1d] and as α_{1a} adrenergic receptor antagonists.[1e]

The chemical properties of the oxo group are similar to those of the ylidenemalononitrile fragment (Fig. 1).[2] Therefore, as a potential bioactive compound, 2-(dicyanomethylene)-1,2-dihydropyridine (**2**) might be interesting as a structural analog of compound **1**. Metal complexes of compounds with the general formulas **1** and **2** are important in optical recording media.[3]

In this Letter, we describe a new approach to 2-(dicyanomethylene)-1,2-dihydropyridine derivatives **5**–**8** using the base-initiated reaction between 1,3-dicarbonyl compounds **3** and arylmethylidene derivatives **4** of malononitrile dimer[4] (Scheme 1 and Table 1).

The reaction is thought to involve the Michael addition of 1,3-dicarbonyl compounds **3** to the arylmethylidene derivatives **4** of malononitrile dimer (Scheme 2). Subsequent cyclization of the amino group to the carbonyl group leads to the formation of intermediate **A**. Elimination of water then leads to the formation of 4-aryl-3-cyano-2-(dicyanomethyl)-6-methyl-1,2,3,4-tetrahydropyridin-2-ide salt **5**, which in some cases can be isolated in yields of 57–75%.[5]

The salts **5** probably exist in equilibrium with 4-aryl-5-cyano-6-(dicyanomethylene)-2-methyl-1,4,5,6-tetrahydropyridine derivatives **6**, which can be easily dehydrogenated into the final 4-aryl-5-cyano-6-(dicyanomethylene)-2-methyl-1,6-dihydropyridine derivatives **7**. This may explain the low yields of compounds **5** and **6**.

The synthesis of compounds **6** and **7** in one step would be useful in order to avoid the isolation of compound **5**. Mono-, di-, and tripotassium or sodium phosphate was used as the base for the

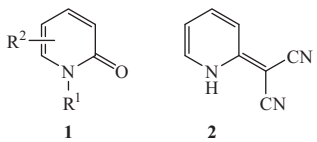

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Figure 1. Pyridin-2-ones **1** and 2-(dicyanomethylene)-1,2-dihydropyridine (**2**).

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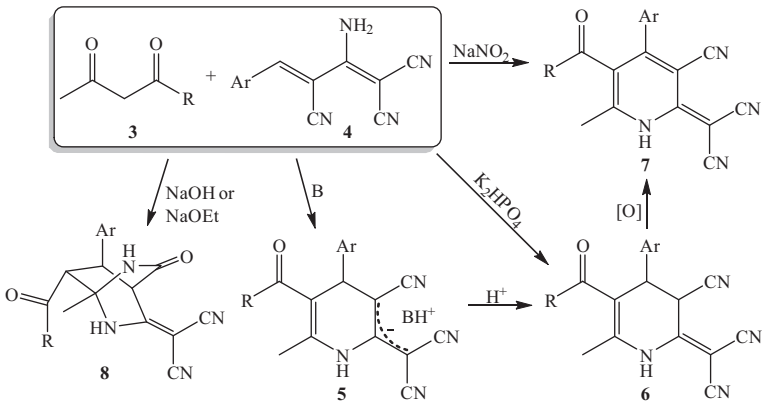


Scheme 1. Michael addition 1,3-dicarbonyl compound **3** to the arylmethylidene derivatives **4** of malononitrile dimer.

Table 1
Synthesis of compounds 5-8

Reagent	R	Substrate	Ar	Product	Yield[a] (%)			
					5	**6**	**7**	**8**
3a	OC_2H_5	**4a**	C_6H_5	**a**	62	67	64	38
3a	OC_2H_5	**4b**	2-ClC_6H_4	**b**	70	–	67	29
3a	OC_2H_5	**4c**	4-FC_6H_4	**c**	65	–	71	26
3a	OC_2H_5	**4d**	4-$H_3CC_6H_4$	**d**	57	–	–	–
3a	OC_2H_5	**4e**	4-$(CH_3)_2NC_6H_4$	**e**	–	–	60	35
3a	OC_2H_5	**4f**	3-BrC_6H_4	**f**	–	–	74	–
3b	OCH_3	**4a**	C_6H_5	**g**	66	63	69	40
3b	OCH_3	**4d**	4-$H_3CC_6H_4$	**h**	–	90	63	–
3b	OCH_3	**4c**	4-FC_6H_4	**i**	–	93	71	–
3b	OCH_3	**4f**	3-BrC_6H_4	**j**	–	–	80	–
3c	NH_2	**4a**	C_6H_5	**k**	–	83	76	45
3c	NH_2	**4b**	2-ClC_6H_4	**l**	–	–	81	–
3c	NH_2	**4d**	4-$H_3CC_6H_4$	**m**	–	–	85	–
3d	CH_3	**4a**	C_6H_5	**n**	75	–	68	–
3e	$N(CH_3)_2$	**4a**	C_6H_5	**o**	–	–	65	42
3f	NHPh	**4a**	C_6H_5	**p**	–	89	78	–
3g	Ph	**4a**	C_6H_5	**q**	–	94	77	–
3g	Ph	**4d**	4-$H_3CC_6H_4$	**r**	–	–	62	–
3g	Ph	**4f**	3-BrC_6H_4	**s**	–	–	74	–

[a] Yield of isolated product.

formation of compound **6**.[6] The formation of compound **7** in one step is possible using sodium nitrite as the base.[7] Apparently, sodium nitrite functions as both the basic catalyst and the oxidant.[8]

The structures of compounds **5–7** were confirmed by IR, ^1H and ^{13}C NMR spectroscopy, mass spectrometry, and by X-ray diffraction analysis of compound **7n** (Fig. 2).[9]

The reaction of compounds **3** and **4** under catalysis by a strong base proceeds via an alternative intramolecular process, that leads to the formation of methyl and ethyl 8-aryl-3-(dicyanomethylene)-1-methyl-5-oxo-2,6-diazabicyclo[2.2.2]octane derivatives **8** (Scheme 3) in yields of 26–45%.[10]

It is assumed that under the action of a strong base, there is the possibility of formation of intermediate **B**. In intermediate **B**, depending on the relative positions of the hydroxy and cyano

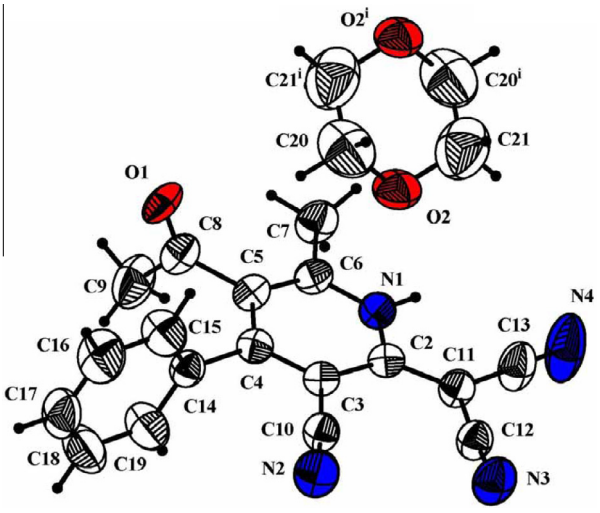
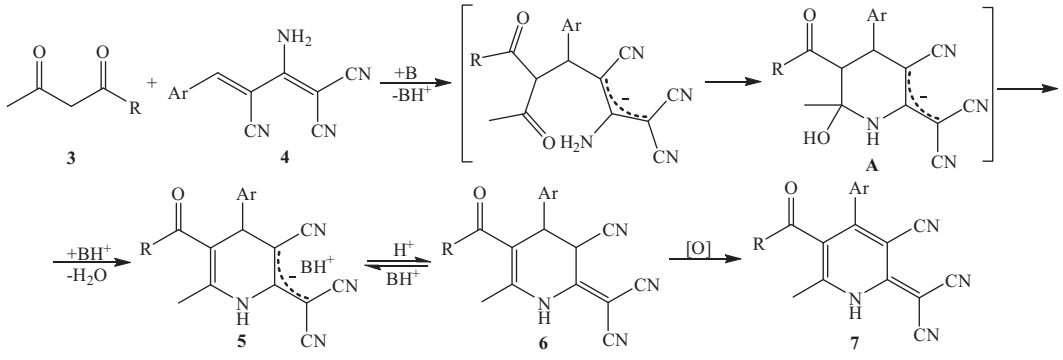
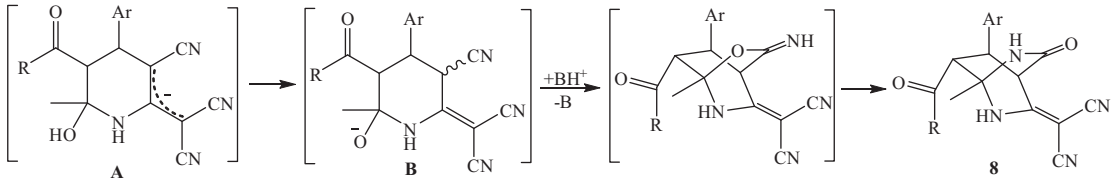


Figure 2. ORTEP diagram of 2-[5-acetyl-3-cyano-6-methyl-4-phenylpyridin-2(1*H*)-ylidene]malononitrile (**7n**) as a solvate with 1,4-dioxane.



Scheme 2. Proposed mechanism for the synthesis of compounds **5–7**.



Scheme 3. Proposed mechanism for the synthesis of 2,6-diazabicyclo[2.2.2]octanes **8**.

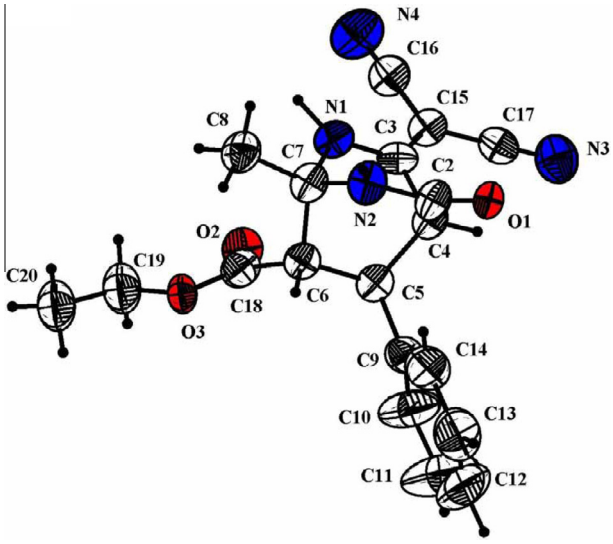


Figure 3. ORTEP diagram of ethyl (7*R**,8*S**)-3-(dicyanomethylene)-1-methyl-5-oxo-8-phenyl-2,6-diazabicyclo[2.2.2]octane-7-carboxylate (**8a**).

groups, there may be a flagpole interaction and formation of a pyran ring. Iminolactone-lactam rearrangement then leads to compounds **8**,[11] which contain four asymmetric centers. In our case, according to ^{1}H NMR and ^{13}C NMR spectroscopy (**8a**), only one diastereomer was observed. An unambiguous determination of the position of the substituents was achieved by X-ray diffraction analysis using a single crystal of compound **8a** (Fig. 3).[12]

In conclusion, 2-(dicyanomethylene)-1,2-dihydropyridine derivatives have been obtained for the first time, as a result of a domino process in one synthetic operation between 1,3-dicarbonyl compounds **3** and the arylmethylidene derivatives of malononitrile dimer **4**. Our goal is further modification of the substituents and a study of the biological activity of these products.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.03.056.

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3. Clariant International Ltd. WO 2006/10773; 2006; *Chem. Abstr.* 2006, *144*, 172705
4. (a) Junek, H.; Wolny, B. *Monatsh. Chem.* **1976**, *107*, 999–1006; (b) Gazit, A.; Yaish, P.; Gilon, Ch.; Levitzki, A. *J. Med. Chem.* **1989**, *32*, 2344–2352. *Typical procedure for the preparation of arylmethylidene derivatives of malononitrile dimer **4a–f***. A mixture of the appropriate aromatic aldehyde (10 mmol), malononitrile dimer (10 mmol), and piperidine acetate (0.1 mmol) in EtOH (50 mL) was stirred at 70 °C for 15–20 min. After cooling, the resulting precipitate was filtered and washed with *i*-PrOH.
5. *Typical procedure for the preparation of 4-aryl-3-cyano-2-(dicyanomethyl)-6-methyl-1,2,3,4-tetrahydropyridin-2-ide salts **5***. A mixture of 1,3-dicarbonyl compound **3** (10 mmol), 2-amino-4-arylbuta-1,3-diene-1,1,3-tricarbonitrile (**4**) (10 mmol), and diethylamine (12 mmol) in EtOH (10 mL) was heated at reflux temperature with vigorous stirring for 8–10 min. After cooling, the resulting precipitate was filtered, washed with *i*-PrOH and recrystallized from refluxing EtOAc. Piperidine (12 mmol) was used as the base for the synthesis of compound **5g** instead of diethylamine. Compound **5a**. Mp 164–165 °C; ^{1}H NMR (500.13 MHz, DMSO-d_6): δ 1.11 (3H, t, J = 7.0 Hz, CH_3), 1.16 (6H, t, J = 7.2 Hz, $2CH_3$), 2.28 (3H, s, CH_3), 2.93 (4H, q, J = 7.2 Hz, $2CH_2$), 3.97 (2H, q, J = 7.1 Hz, CH_2), 4.29 (1H, s, CH), 7.08 (2H, d, J = 7.3 Hz, C_6H_5), 7.14 (1H, t, J = 7.3 Hz, C_6H_5), 7.24 (2H, t, J = 7.6 Hz, C_6H_5), 8.07 (1H, s, NH), 8.14 (1H, br s, NH_2^+). ^{13}C NMR (125.76 MHz, DMSO-d_6): δ 10.93, 14.04, 18.58, 39.73, 41.03, 41.31, 58.91, 67.56, 100.92, 122.06, 122.12, 126.00, 126.38, 128.08, 145.99, 147.10, 147.34, 166.57. IR (mineral oil, cm^{-1}): 3279–3169 (NH), 2220, 2167 (CN), 1685 (C=O), 1580 (C=C). MS (EI, 70 eV): m/z (%) 332 $[M]^+$ (21). Anal. Calcd for $C_{23}H_{27}N_5O_2$: C, 68.13; H, 6.71; N, 17.27. Found: C, 67.96; H, 6.94; N, 17.23.
6. *Typical procedure for the preparation of 4-aryl-5-cyano-6-(dicyanomethylene)-2-methyl-1,4,5,6-tetrahydropyridine derivatives **6a,g***. A mixture of 1,3-dicarbonyl compound **3** (10 mmol), 2-amino-4-arylbuta-1,3-diene-1,1,3-tricarbonitrile (**4**) (10 mmol), and K_2HPO_4 (12 mmol) in EtOH (70 mL) was refluxed for 3–4 h. After completion of the reaction (TLC), the solution was filtered and neutralized with 25% HCl (to pH = 4). The resulting precipitate was filtered and washed with *i*-PrOH and Et_2O. Compound **6a**. Mp 141–142 °C (dec.); ^{1}H NMR (500.13 MHz, DMSO-d_6): δ 1.13 (3H, t, J = 7.1 Hz, CH_3), 2.57 (3H, s, CH_3), 4.10 (2H, dq, J = 7.1, 3.0 Hz, CH_2), 4.55 (1H, d, J = 2.1 Hz, CH), 4.62 (1H, br s, CH), 7.24 (2H, d, J = 7.3 Hz, C_6H_5), 7.31 (1H, t, J = 7.3 Hz, C_6H_5), 7.37 (2H, t, J = 7.4 Hz, C_6H_5), 11.26 (1H, s, NH). ^{13}C NMR (125.76 MHz, DMSO-d_6): δ 13.87, 17.53, 34.77, 39.11, 59.67, 60.45, 106.99, 111.55, 113.07, 115.32, 126.80, 128.13, 128.94, 136.01, 146.10, 156.13, 164.99. IR (mineral oil, cm^{-1}): 3240–3123 (NH), 2227, 2210 (CN), 1704 (C=O), 1589 (C=C). MS (EI, 70 eV): m/z (%) 332 $[M]^+$ (16), 259 $[M-73]^+$ (53). Anal. Calcd for $C_{19}H_{16}N_4O_2$: C, 68.66; H, 4.85; N, 16.86. Found: C, 68.78; H, 4.80; N, 16.87. *Typical procedure for the preparation of 4-aryl-5-cyano-6-(dicyanomethylene)-2-methyl-1,4,5,6-tetrahydropyridine derivatives **6h,i,k,p,q***. A solution of compound **5** (10 mmol) in a mixture of 1,4-dioxane (15 mL) and H_2O (30 mL) was neutralized with 5% H_2SO_4. The resulting precipitate was filtered and washed with H_2O, and then recrystallized from a mixture of 1,4-dioxane:H_2O.
7. *Typical procedure for the preparation of 4-aryl-5-cyano-6-(dicyanomethylene)-2-methyl-1,6-dihydropyridine derivatives **7***. A mixture of 1,3-dicarbonyl compound **3** (10 mmol), 2-amino-4-arylbuta-1,3-diene-1,1,3-tricarbonitrile (**4**) (10 mmol) ,and $NaNO_2$ (12 mmol) in EtOH (70 mL) was refluxed for 5–6 h. After completion of the reaction (TLC), the solution was filtered and neutralized with 1% HCl (to pH = 4). The precipitate was triturated with H_2O (20 mL), filtered, and washed with H_2O (40 mL), and then recrystallized from a mixture of 1,4-dioxane:*i*-PrOH. Compound **7a**. Mp 224–225 °C (dec.); ^{1}H NMR (500.13 MHz, DMSO-d_6): δ 0.72 (3H, t, J = 7.1 Hz, CH_3), 2.39 (3H, s, CH_3), 3.82 (2H, q, J = 7.1 Hz, CH_2), 6.66 (1H, br s, NH), 7.24-7.28 (2H, m, C_6H_5), 7.46 (3H, t, J = 3.2 Hz, C_6H_5). ^{13}C NMR (125.76 MHz, DMSO-d_6): δ 13.23, 21.92, 42.39, 60.80, 94.27, 115.05, 118.20, 119.86, 127.92, 128.34, 129.18, 136.22, 155.55, 156.51,

158.35, 165.91. IR (mineral oil, cm^{-1}): 3232–3080 (NH), 2220, 2204 (CN), 1720 (C=O), 1607 (C=C). MS (EI, 70 eV): *m*/*z* (%) 330 $[M]^+$ (47), 285 $[M-45]^+$ (86). Anal. Calcd for $C_{19}H_{14}N_4O_2$: C, 69.08; H, 4.27; N, 16.96. Found: C, 69.06; H, 4.45; N, 16.72.

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9. Crystallographic data (excluding structure factors) for the structure 7n in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 973315. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
10. *Typical procedure for the preparation of 8-aryl-3-(dicyanomethylene)-1-methyl-5-oxo-2,6-diazabicyclo[2.2.2]octane derivatives* ***8***. A mixture of 1,3-dicarbonyl compound **3** (10 mmol), 2-amino-4-arylbuta-1,3-diene-1,1,3-tricarbonitrile (**4**) (10 mmol) and NaOEt (12 mmol) in EtOH (10 mL) was refluxed for 1–2 h. After completion of the reaction (TLC), the solution was filtered and neutralized with 1% HCl (to pH = 4). The precipitate was triturated with H_2O (20 mL), filtered, and washed with *i*-PrOH and H_2O (40 mL). NaOMe (12 mmol) in MeOH (10 mL) was used as the base for the synthesis of compound **8g**. Compound **8a**. Mp 264–265 °C (dec.); ^1H NMR (500.13 MHz, DMSO-d_6): δ 1.20 (3H, t, J = 7.1 Hz, CH_3), 1.67 (3H, s, CH_3), 3.34 (1H, d, J = 5.6 Hz, CH), 3.51–3.52 (1H, m, CH), 3.65 (1H, dd, J = 5.6, 2.4 Hz, CH), 4.10-4.18 (2H, m, CH_2), 7.29–7.40 (5H, m, C_6H_5), 9.76 (1H, d, J = 1.6 Hz, NH), 10.89 (1H, s, NH). ^{13}C NMR (125.76 MHz, DMSO-d_6): δ 13.82, 18.85, 43.66, 46.55, 54.15, 57.32, 61.16, 69.59, 114.01, 115.59, 127.44, 127.80, 128.85, 138.51, 166.40, 168.73, 170.01. IR (mineral oil, cm^{-1}): 3321–3156 (NH), 2211 (CN), 1712 (C=O), 1601 (C=C). MS (EI, 70 eV): *m*/*z* (%) 174 $[M-176]^+$ (82), 91 $[M-259]^+$ (8). Anal. Calcd for $C_{19}H_{18}N_4O_3$: C, 65.13; H, 5.18; N, 15.99. Found: C, 65.16; H, 5.22; N, 15.96.
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12. Crystallographic data (excluding structure factors) for the structure **8a** in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 973314. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

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