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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]

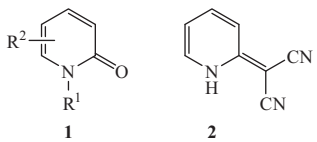
The chemical properties of the oxo group are similar to those of the ylidenemalononitrile fragment (Fig. 1).[2] Therefore, as a potential bioactive compound, 2-(dicyanomethylene)-1,2-dihydropyridine (**2**) might be interesting as a structural analog of compound **1**. Metal complexes of compounds with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



1 2

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

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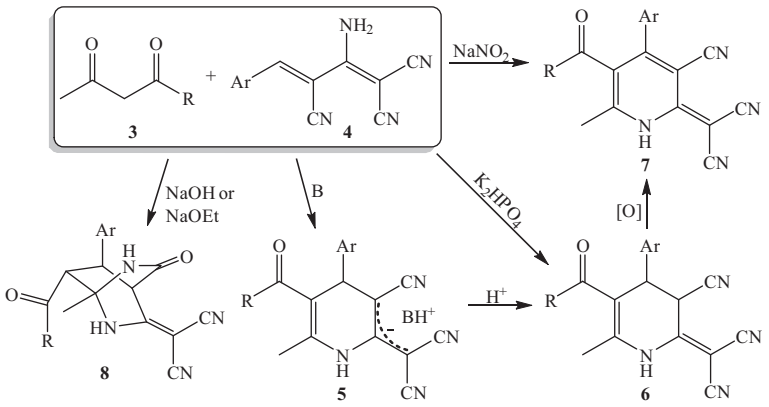


Scheme 1. Michael addition 1,3-dicarbonyl compound **3** to the arylmethylidene derivatives **4** of malononitrile dimer.

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

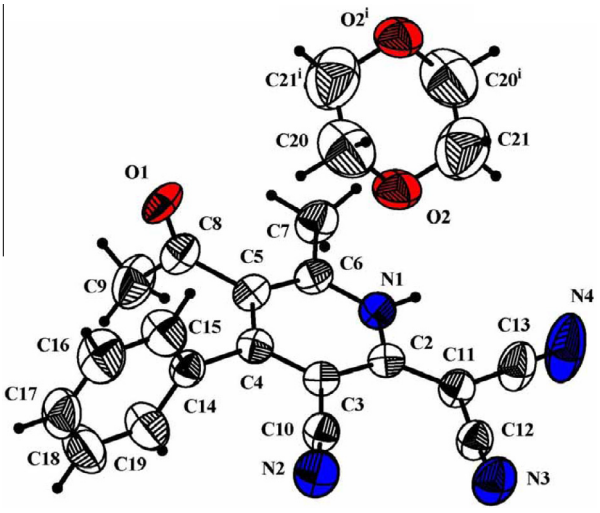
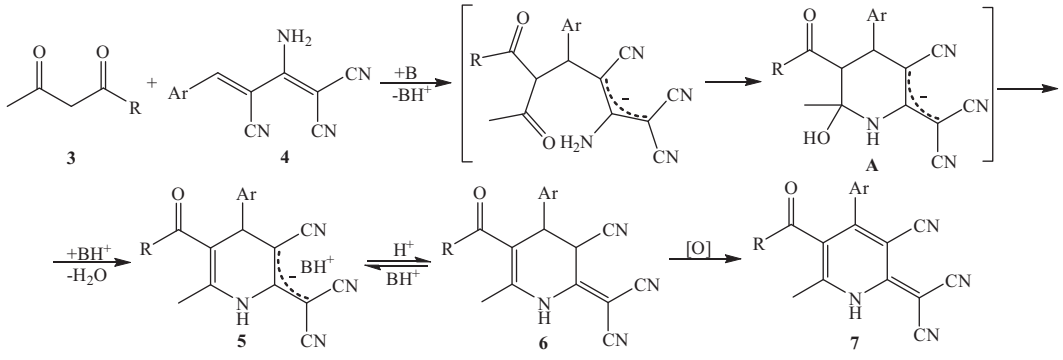


Figure 2. ORTEP diagram of 2-[5-acetyl-3-cyano-6-methyl-4-phenylpyridin-2(1*H*)-ylidene]malononitrile (**7n**) as a solvate with 1,4-dioxane.



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