Synlett V. S. Mityanov and co-workers Letter

Unexpected Aldehyde-Catalyzed Reaction of Imidazole *N*-Oxides with Ethyl Cyanoacetate

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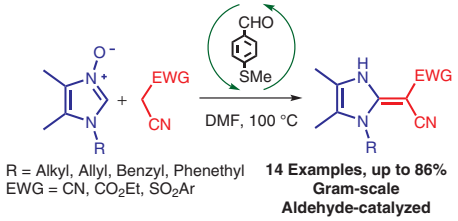

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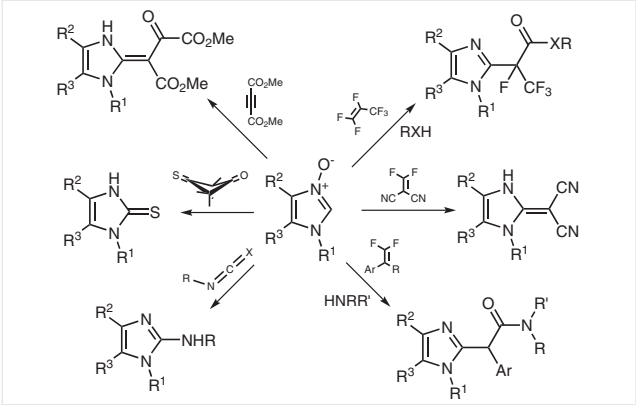
Abstract The reaction of 2-unsubstituted imidazole *N*-oxides with ethyl cyanoacetate and aromatic aldehydes leads to the formation of ethyl 2-cyano-2-(1,3-dihydro-2*H*-imidazole-2-ylidene)acetates. The reaction proceeds through an initial [3+2] cycloaddition, followed by cleavage of the cycloadduct and regeneration of the aldehyde, which essentially plays a catalytic role.

Key words imidazole oxides, 1,3-dipolar cycloaddition, reaction mechanism, organocatalysis, multicomponent reaction, [3+2] cycloaddition

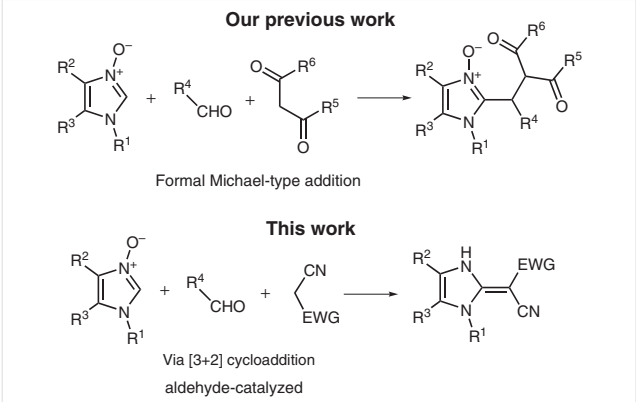
Imidazole *N*-oxides possess a unique reactivity profile that, combined with their availability,[1] makes them valuable intermediates in modern organic synthesis.[1b–d] Particularly attractive is the possibility of C–H functionalization of the heterocyclic core, which permits the use of simple precursors in the synthesis of complex functional heterocycles.

There are several different approaches to C–H functionalization. Among Pd-catalyzed selective cross-coupling reactions,[2a,b] imidazole *N*-oxides readily enter into nucleophilic *cine*-substitution reactions.[3] Of particular interest is the series of [3+2]-cycloaddition processes[3b,4] in which the *N*-oxides of 2-unsubstituted imidazoles act as 1,3-dipoles. The initially formed adducts are very labile, and secondary processes occur, leading to a wide range of products as shown in Scheme 1.

Also, we have previously described[5] the ability of 2-unsubstituted imidazole *N*-oxides to act as C-nucleophiles in Michael-type addition to enones formed by condensation of aldehydes with such classic C–H acids as Meldrum's acid, barbituric acid, or dimedone (Scheme 2).



Scheme 1 Imidazole *N*-oxide functionalizations based on an initial [3+2] cycloaddition



Scheme 2 Reactions of imidazole *N*-oxides with aldehydes and C–H acids

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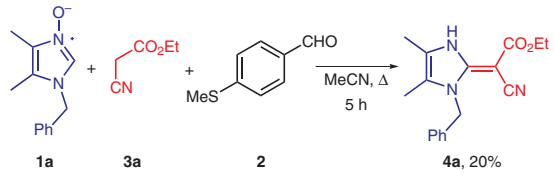
In a continuation of our studies on the reactivity of imidazole *N*-oxides, we proposed to extend this reaction to such C–H acids as ethyl cyanoacetate or malononitrile. However, the reaction of equimolar amounts of the *N*-oxide **1a**, ethyl cyanoacetate (**3a**) and 4-(methylsulfanyl)benzaldehyde (**2**) in acetonitrile unexpectedly led to compound **4a** as the only product in 20% yield after recrystallization from ethanol (Scheme 3).



Scheme 3 Initial experiment

The structure of product **4a** was confirmed by ^{1}H and ^{13}C NMR spectroscopy and HRMS. In the IR spectrum of **4a**, a sharp intense CN absorption band was observed at 2183 cm^{-1}. Single-crystal X-ray analysis also confirmed the structure of **4a** (Figure 1).[6]

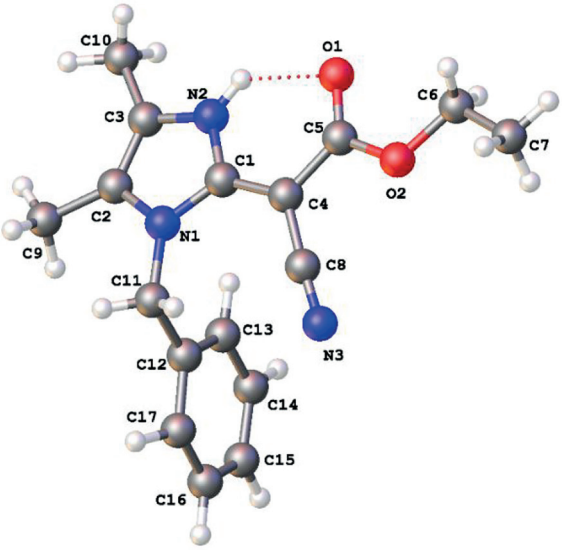
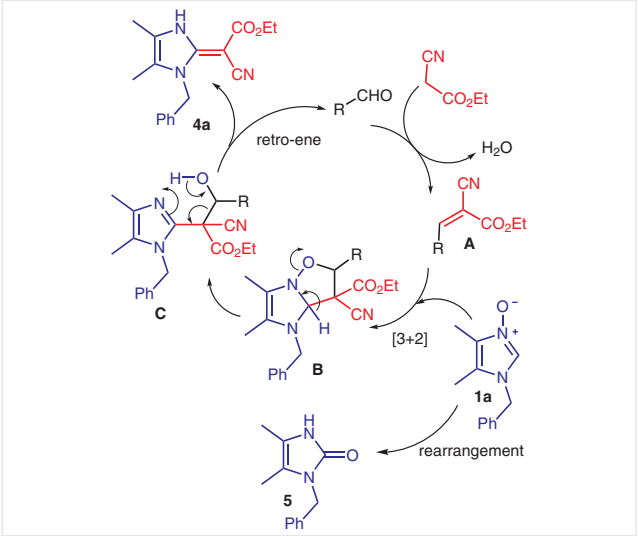


Figure 1 X-ray crystal structure of compound **4a**

Because the product does not contain an aldehyde fragment and because, in the absence of an aldehyde, the reaction between **1a** and **3a** failed, we assumed that the aldehyde performs a catalytic function and that the process proceeds according to the mechanism shown in Scheme 4.

In the first stage, a [3+2] cycloaddition occurs between the ylidene **A** and the *N*-oxide. The initially formed unstable isoxazolidine cycloadduct **B** readily undergoes rearomatization and ring-opening to give intermediate **C**, which undergoes cleavage of the C–C bond with the elimination of the aldehyde (retro-ene reaction).



Scheme 4 Proposed reaction mechanism

To obtain more details, we monitored the process in various solvents (Table 1). The yields of products were determined by HPLC with external standards. It is noteworthy that in all cases, 1-benzyl-4,5-dimethyl-1,3-dihydro-2*H*-imidazol-2-one (**5**) was formed as a byproduct, apparently as a result of thermal rearrangement[7] of the starting *N*-oxide. It was shown that on prolonged heating in various solvents, **5** is inert to aldehyde, ethyl cyanoacetate, and their mixtures. Also, various amounts of the unreacted ylidene derivative ethyl (2*Z*)-2-cyano-3-[4-(methylsulfanyl)phenyl]acrylate (**6**) were detected in all cases. Note that in chloroform (entry 4) and, especially, ethanol (entry 6) as the reaction medium, the reaction showed a significantly different course in which almost all the aldehyde and ethyl cyanoacetate were converted into the ylidene derivative **6**,

Table 1 Reaction Monitoring[a]

Entry	Solvent[b]	Yield (%) of **4a**	Yield (%) of **5**	Conversion of **2**
1	benzene	86	8	0.26
2	PhMe	88	12	0.29
3	1,4-dioxane	42	2	0.62
4	$CHCl_3$	17	0	0.86[c]
5	MeCN	69	2	0.36
6	EtOH	2	0	0.97[c]
7	**DMF[d]**	**96**	**4**	**0.20**

[a] Yields and conversions were determined by HPLC analysis.
[b] Reaction was carried out at the reflux temperature unless otherwise stated.
[c] **6** was the major product.
[d] At 100 °C.

but interaction with the *N*-oxide did not occur. When a similar effect was reported for the reaction of imidazole *N*-oxides with 1,1-difluorostyrenes in methanol,[4f] the authors suggested that the low reactivity of the *N*-oxide was caused by hydrogen bonding and solvation by MeOH. It is possible that residual HCl might have had an effect in the case of chloroform. The highest yield of the desired product was obtained in DMF (entry 7), when the conversion of the aldehyde was only 20%.

To reveal the catalytic role of the aldehyde **2** more clearly, we carried out a series of experiments using it in reduced amounts. The results are summarized in Table 2. However, although just 5 mol% of the aldehyde led to the formation of the product in 48% yield, the amount of the imidazole-2-one byproduct also increased (Table 2, entry 4). Furthermore, increasing duration of the reaction led to a significant resinification of the reaction mixture, and the conversion of starting *N*-oxide did not exceed 50%. Also, the process was not affected by replacing 4-(methylsulfanyl)benzaldehyde (**2**) with benzaldehyde, but the use of formaldehyde (in the form of an aqueous solution) or acetaldehyde led to the formation of a complex mixture of unidentified byproducts.

Table 2 Monitoring of the Effects of the Amount of Aldehyde[a]

Entry	**2** (mol%)	Time (h)	Yield (%) of **4a**	Yield (%) of **5**
1	20	4	36	1
2	20	16	54	3
3	5	4	2	0
5	5	16	48	13

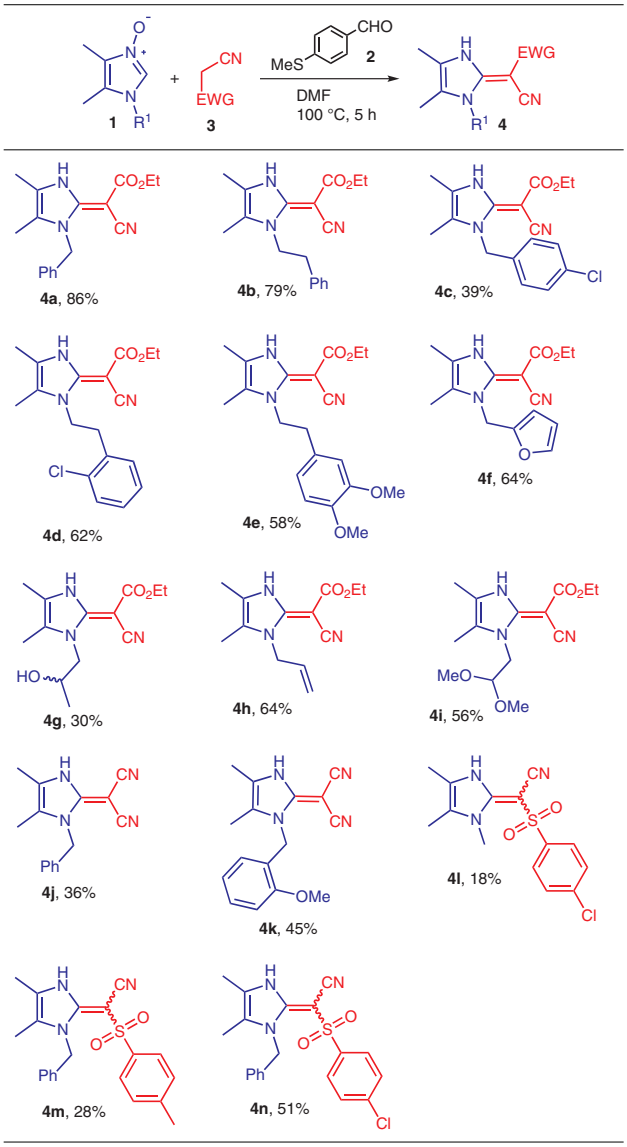
[a] Yields and conversions were determined by HPLC analysis.

Under optimal conditions (Table 1, entry 7), a number of derivatives were obtained from various 2-unsubstituted imidazole *N*-oxides **1**. Besides ethyl cyanoacetate, malononitrile (**3b**), 2-tosylacetonitrile (**3c**), and 2-[(4-chlorophenyl)sulfonyl]acetonitrile (**3d**) were used as C–H acids (Table 3).[8] In the case of derivative **4i**, we showed that even the labile acetal group was inert under the reaction conditions.

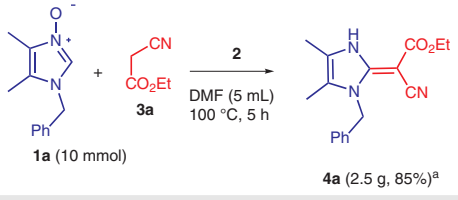
Although the configuration of the CN and CO_2Et groups in compounds **4a–i** is apparently the same as that in **4a** (which is assumed to exist as the *E*-isomer as a result of the possibility of strong intramolecular hydrogen bonding and from X-ray crystallography data), this problem has not been investigated for derivatives **4l–n**; however, NMR studies suggested that all compounds **4** exist as single diastereomers.

Furthermore, under the optimized conditions, gram-scale quantities of compound **4a** were obtained in 85% isolated yield (Scheme 5), indicating the utility of our transformation as a synthetic method.

Table 3 Reaction Scope[a,b]

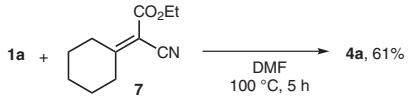


[a] Reaction conditions: **1** (2 mmol), **3** (2 mmol), **2** (2 mmol), DMF (4 mL), 100 °C, 5 h.
[b] Isolated yields are reported.



Scheme 5 Gram-scale synthesis of **4a**. When the reaction was complete, the solvent was removed under vacuum and the residue was crystallized from EtOAc to give pure **4a**.

Note that the previously obtained ylidene **7**, based on cyclohexanone, can also be introduced into the reaction to give **4a** in 61% yield (Scheme 6). However, 1,1-difluoroalkenes containing an aliphatic instead of an aromatic substituent have been shown to be completely inert with respect to the imidazole *N*-oxide, even under rather harsh conditions (DMF, 100 °C, 7 d).[4f]



Scheme 6 Reaction of *N*-oxide **1a** with ethyl cyano(cyclohexylidene)-acetate (**7**)

In summary, therefore, we have identified the possibility of condensation of 2-unsubstituted imidazole *N*-oxides with ethyl cyanoacetate and related nitriles in the presence of an aromatic aldehyde that plays the role of a catalyst. Further investigations of this reaction are currently ongoing.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1691527.

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(6) CCDC 1948977 contains the supplementary crystallographic data for compound **4a**. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

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(8) **Compounds 4a–n; General Procedure**

A solution of the appropriate imidazole *N*-oxide **1** (1 mmol), nitrile **3** (1 mmol), and aldehyde **2** (1 mmol) in DMF (4 mL) was stirred at 100 °C for 5 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (silica gel, EtOAc).

Ethyl (2*E*)-(1-Benzyl-4,5-dimethyl-1,3-dihydro-2*H*-imidazol-2-ylidene)(cyano)acetate (4a)

White solid; yield: 255 mg (86%); mp 164–166 °C. IR (KBr): 3208, 2983, 2183 (CN), 1639, 1568, 1475, 1440, 1369, 1321, 1305, 1261, 1248, 1209, 1132, 1087, 1034, 975, 779, 732, 705, 693, 533, 457 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 11.91 (s, 1 H), 7.40–7.25 (m, 2 H), 7.05 (d, *J* = 7.1 Hz, 3 H), 5.41 (s, 2 H), 4.06 (q, *J* = 7.1 Hz, 2 H), 2.12 (s, 3 H), 1.95 (s, 3 H), 1.17 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR (151 MHz, DMSO-d_6): δ = 168.40, 145.23, 136.31, 128.72, 127.44, 126.61, 125.98, 121.11, 120.75, 120.08, 58.38, 46.33, 14.71, 8.91, 7.85. HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_{17}H_{20}N_3O_2$: 298.1555; found: 298.1550.

(1-Benzyl-4,5-dimethyl-1,3-dihydro-2*H*-imidazol-2-ylidene)[(4-chlorophenyl)sulfonyl]acetonitrile (4n)

White solid; yield: 204 mg (51%); mp 203–205 °C. IR (KBr): 3294, 2160 (CN), 1651, 1558, 1474, 1435, 1389, 1335, 1312, 1296, 1273, 1142, 1088, 1049, 1011, 933, 825, 795, 756, 717, 633, 579, 478 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 12.44 (s, 1 H), 7.58 (d, *J* = 11.1 Hz, 2 H), 7.49 (d, *J* = 11.2 Hz, 2 H), 7.34–7.06 (m, 3 H), 6.81 (d, *J* = 8.1 Hz, 2 H), 5.22 (s, 2 H), 2.15 (s, 3 H), 1.94 (s, 3 H). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 147.63, 143.24, 138.95, 138.03, 132.00, 131.47, 130.39, 129.49, 128.84, 126.46, 126.01, 122.83, 54.62, 49.75, 11.86, 11.04. HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_{20}H_{19}ClN_3O_2S$: 400.0886; found: 400.0881.

