Rearrangement of Pyran Derivatives Obtained from Vinyl Malononitriles and Aldehydes via Vinylogous Aldol Reaction: A Novel Facile Method for the Synthesis of Dienamides

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Abstract: A novel one-pot approach to a variety dienamides from vinyl malononitriles and aldehydes via vinylogous aldol reaction was achieved by the electrolytic ring opening of the initially formed pyran derivatives under mild basic catalysis with good diastereoselectivity.

Key words: vinyl malononitrile, vinylogous aldol reaction, pyran rearrangement, dienamides

Dienamides have been long recognized as key reactive intermediates due to their great diversity, synthetic potential, and occurrence in nature. Dienamides have been effectively used both as electron-rich and electron-poor dienes in Diels–Alder reactions.[1] Dienamide based Diels–Alder reactions are regioselective and have also been used recently in asymmetric cycloadditions.[2] Acyclic dienamides are also the key constituents in a number of biologically active natural products and pharmaceutically relevant units. Examples of these include apicularen A, salicylihalamide A, zampanolide (Figure 1).[3] Although a number of preparative methods for dienamides have appeared in the literature[4–11] mainly employing isocyanates as substrates and transition metals as catalysts, the development of mild synthetic approaches enabling facile access to these dienamides is desirable.

The vinylogous aldol reaction of α,β-unsaturated carbonyl compounds represents an extension of the classical aldol condensation particularly important both from the preparative and stereochemical point of view.[12]

Recently, Chen et al. reported that α,α-dicyanoolefin compounds can selectively behave as acceptors[13] or vinylogous donors[14,15] in Michael reactions under easily controllable conditions, and yet a simple tertiary amine can smoothly catalyze the Michael addition of an α,α-dicyanoolefin substrate to nitrostyrene by deprotonating the acidic γ-allylic C–H to generate the nucleophilic carbanion.[14a,c] However, vinyl malononitriles have been used extensively in Michael reactions as vinylogous donors, their reactivity in aldol reaction has not yet been explored to any great extent.

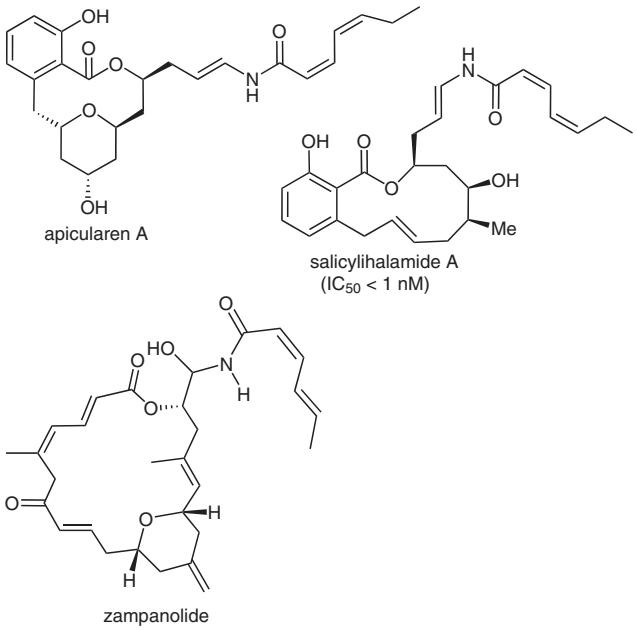

Figure 1 Some natural products with dienamide unit

During our studies on the reactivity of vinyl malononitriles in Michael addition reaction,[16] we found that the vinyl malononitriles also undergo aldol reaction with isatin derivatives forming aldol adducts which are susceptible to intramolecular nucleophilic addition and isomerization furnishing spirofused polyhydro isochromene derivatives with good diastereoselectivity under mild basic catalysis.[17] The success of our efficient novel tandem synthesis of spirofused polyhydroisochromenes encouraged us to explore this methodology for aldehydes also.

Interestingly the pyran derivatives obtained initially from vinyl malononitriles and aldehydes by this methodology underwent electrolytic ring opening to afford a variety of five- to eight-membered stereodefined cyclic dienamides in mild reaction conditions.[18]

The strategy we have developed begins with the reaction of 1.5 mmol of cyclohexylidene malononitrile (**1a**, Figure 2) and 1 mmol of 4-chlorobenzaldehyde (**2a**) in ethylene glycol at room temperature (32 °C) in the presence of 1 mmol of triethylamine. The reaction undergoes smoothly within 30 minutes yielding 50% of the product. Elevation from room temperature to 40 °C increases the yield upto 78% (Scheme 1). The product was isolated as a

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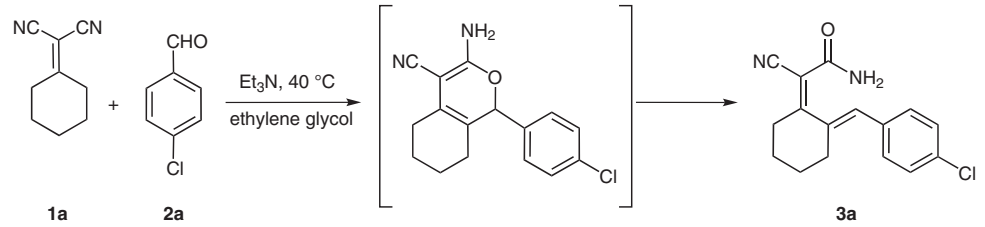
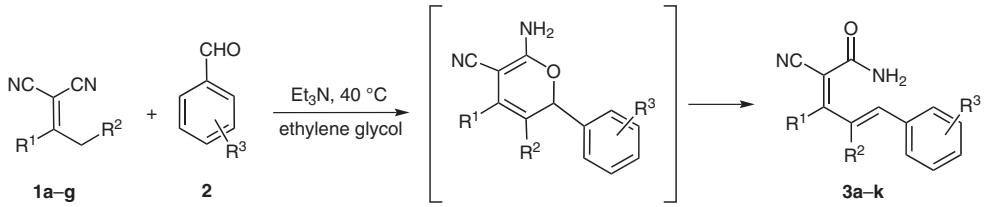


Scheme 1



Scheme 2

single diastereomer by column chromatography and assigned the structure **3a** on the basis of spectroscopic data.[19] In the ^{1}H NMR spectra the olefinic proton appears at δ = 6.40 ppm, whereas the amide NH_2 protons resonated at δ = 7.53 and 7.87 ppm as two singlets. The amide carbon in ^{13}C signaled at δ = 164.5 ppm. Further the stereochemistry of **3a** was determined as (2*Z*,4*E*) based on its crystal structure (Figure 3).[20]

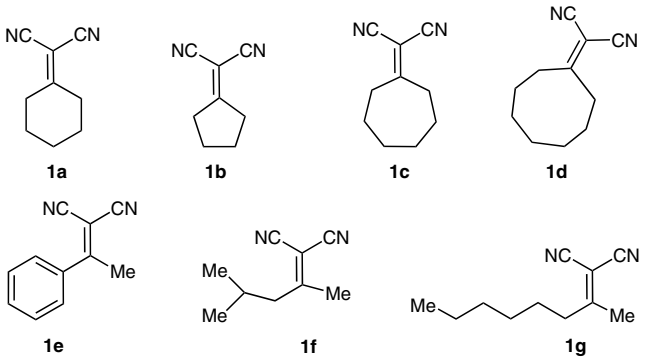


Figure 2

Similarly the stereochemistries of **3b–k** were assigned analogously to those of **3a**. In the ^{1}H NMR, the two olefinic protons of acyclic dienamides **3i–k** showed the *trans* coupling constant 16 Hz.

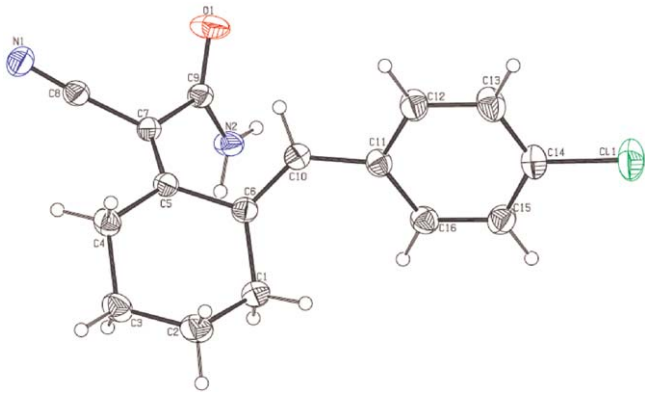


Figure 3 ORTEP diagram of compound **3a**

With the demonstration of the utility of this protocol in general, we attempted a series of reactions with a variety of vinyl malononitriles and aromatic aldehydes under mild reaction conditions. It is note worthy that all dienamides showed excellent diastereoselectivity (Scheme 2 and Table 1). However, the reaction of vinyl malononitriles with aliphatic aldehydes was unsuccessful.

To the best of our knowledge this is the first report of the preparation of dienamides using vinyl malononitriles.

Table 1 Synthesis of Dienamides via Vinylogous Aldol Reaction

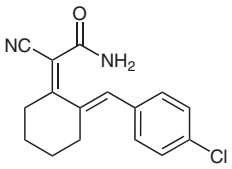
Entry	Vinyl malononitrile	R^3	Dienamide	Time (min)	Yield (%)[a]
1	**1a**	4-Cl	**3a** 	40	78

Table 1 Synthesis of Dienamides via Vinylogous Aldol Reaction (continued)

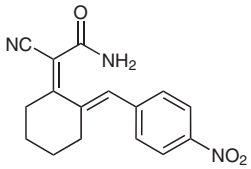
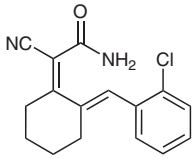
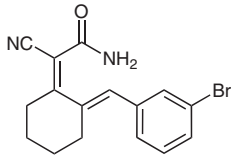
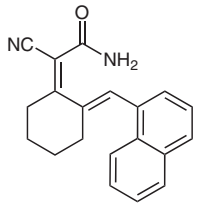
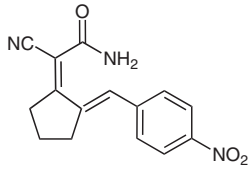
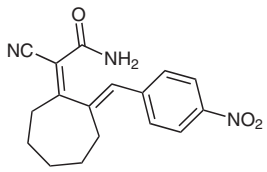
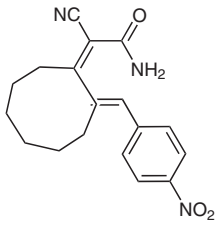
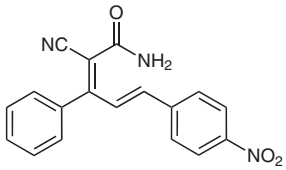
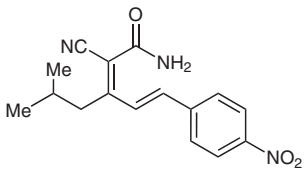
Entry	Vinyl malononitrile	R^3	Dienamide	Time (min)	Yield (%)[a]
2	**1a**	4-NO_2	**3b** 	35	81
3	**1a**	2-Cl	**3c** 	45	75
4	**1a**	3-Br	**3d** 	50	75
5	**1a**	C_4H_4	**3e** 	60	70
6	**1b**	4-NO_2	**3f** 	35	80
7	**1c**	4-NO_2	**3g** 	45	75
8	**1d**	4-NO_2	**3h** 	50	70
9	**1e**	4-NO_2	**3i** 	35	80
10	**1f**	4-NO_2	**3j** 	30	85

Table 1 Synthesis of Dienamides via Vinylogous Aldol Reaction (continued)

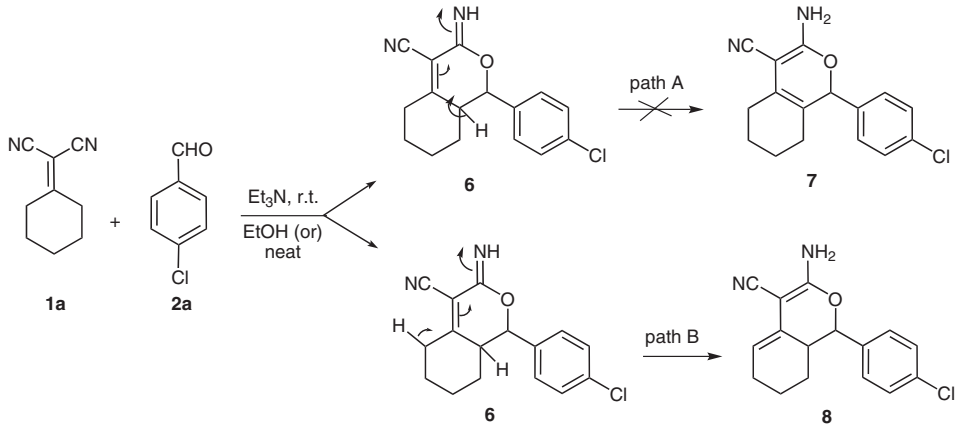
Entry	Vinyl malononitrile	R^3	Dienamide	Time (min)	Yield (%)[a]
11	**1g**	4-NO_2	**3k**	40	80

[a] Isolated yield.

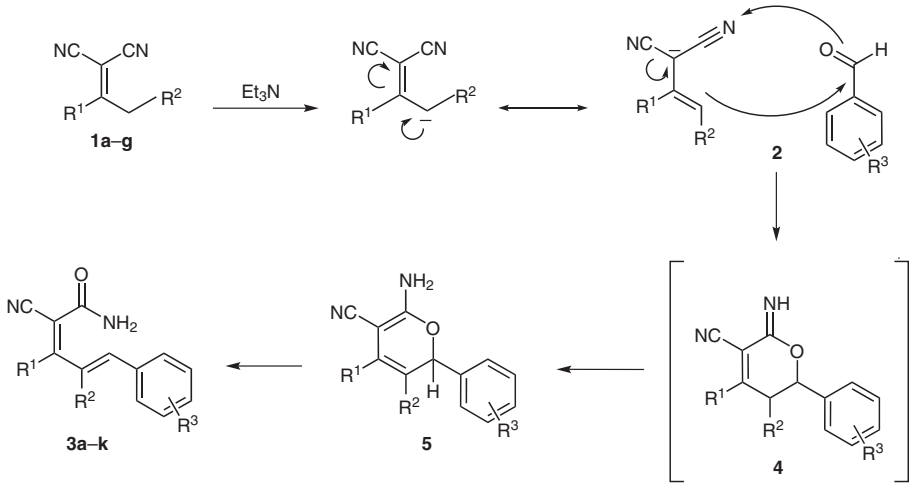
When the reaction of **1a** with **2a** was carried out in ethanol and in neat conditions, interestingly methylene hydrogen of intermediate **6** was isomerized resulting in the isolation of polyhydroisochromene derivative **8** in 60% yield by simple filtration (Scheme 3). But when the reaction was carried out with other vinyl malononitriles (**1b–g**) a mixture of inseparable products was obtained. Compound **8** was found to be stable even when heated in ethanol or ethylene glycol as confirmed by NMR and IR spectroscopy.

Although the detailed mechanism of the above reaction has not been clarified, the formation of the products can be tentatively explained by the pathway presented in Scheme 4. The first step involves facile deprotonation of vinyl malononitrile to furnish a nucleophile that attacks the aldehyde via vinylogous aldol reaction and subsequent intramolecular nucleophilic addition and isomerization resulted in the intermediate **5**. Ultimately intermediate **5** furnished the electrolytic ring-opened cycloadducts (**3a–k**). During our investigations a small fraction of the intermediate **4** (reaction between **1a** and **2a**) was isolated and confirmed by ^{1}H NMR spectroscopy.

Advantages of this method are mild reaction conditions, short reaction times, and isocyanate-free synthesis of dienamides with good diastereoselectivity.



Scheme 3



Scheme 4 Plausible mechanism

In conclusion we have developed a novel simple method for the formation dienamides from readily available starting materials such as vinyl malononitriles and aldehydes via vinylogous aldol reaction followed by the electrolytic cleaveage of pyran ring in one-pot procedure. Further exploration of these dienamides is under way.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(19) **General Procedure for the Synthesis of Dienamide 3a**
The mixture of vinyl malononitrile **1a** (1.5 mmol), aldehyde **2a** (1 mmol), and Et_3N (1 mmol) in ethylene glycol (7 mL) was stirred at 40 °C for 40 min. After the reaction was complete as indicated by TLC, the reaction mixture was cooled to r.t. diluted with acid H_2O (10 mL). The resulting precipitate was filtered and subjected to chromatographic purification over silica gel (Merck; 100–200 mesh; EtOAc–hexane = 3:7) to obtain dienamide **3a** (78%) as a single diastereomer.
Spectral Data of Dienamide 3a (Table 1, Entry 1)
Off-white solid; yield 78%; mp 392 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.55 (m, 2 H), 1.75 (m, 2 H), 2.53 (m, 4 H), 6.42 (s, 1 H), 7.21 (d, *J* = 8.4 Hz, 2 H), 7.38 (d, *J* = 8.4 Hz, 2 H), 7.53 (s, 1 H, D_2O exchangeable), 7.87 (s, 1 H, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 26.0, 26.4, 29.9, 35.1, 106.6, 116.8, 127.2, 128.9, 128.9, 130.1, 131.4, 132.6, 135.0, 139.3, 164.3, 164.5. IR (KBr): ν_{max} = 3397, 3385, 2935, 2216, 1673, 1388, 1092, 626 cm^{-1}. ESI-MS: 287 [M + 1]. Anal. Calcd (%) for $C_{16}H_{15}ClN_2O$: C, 67.02; H, 5.27; N, 9.77. Found: C, 66.97; H, 5.21; N, 9.71.
Spectral Data of Dienamide 3k (Table 1, Entry 11)
Off-white solid; yield 80%; mp 364 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.9 Hz, 3 H), 1.32 (m, 4 H), 1.47 (m, 2 H), 1.64 (m, 2 H), 2.82 (t, *J* = 8.4 Hz, 2 H), 5.87 (s, 1 H, D_2O exchangeable), 6.33 (s, 1 H, D_2O exchangeable), 7.17 (d, *J* = 16.9 Hz, 1 H), 7.69 (d, *J* = 8.4 Hz, 2 H), 8.22 (d, *J* = 8.4 Hz, 2 H), 8.58 (d, *J* = 16.1 Hz. 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1, 22.5, 29.5, 30.3, 31.4, 33.8, 105.6, 117.8, 124.2, 124.2, 128.0, 128.7, 128.7, 137.1, 141.9, 148.2, 163.1, 166.0. IR (KBr): ν_{max} = 3358, 3187, 2930, 2217, 1670, 1600, 1521, 1338 cm^{-1}. ESI-MS: 328 [M + 1]. Anal. Calcd (%) for $C_{18}H_{21}N_3O_3$: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.01; H, 6.43; N, 12.77.

(20) Crystallographic data for compound **3a** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplemental publication No. CCDC- 775677. Copies of the data can be obtained, free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (1223)336033 or email: deposit@ccdc.cam.ac.uk].