Tetrahedron Letters 52 (2011) 6649–6651

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

An efficient organocatalytic method for tandem synthesis of functionalized 2-pyridones

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ARTICLE INFO

Article history:
Received 13 April 2011
Revised 26 September 2011
Accepted 7 October 2011
Available online 14 October 2011

Keywords:
Primary amine
Acetylenic ester
2-Pyridone
MCRs
Tandem reaction

ABSTRACT

Highly functionalized 2-pyridones are obtained via a tandem reaction between primary amines and acetylenic esters in the presence of *N*-methylimidazole as an organocatalyst.

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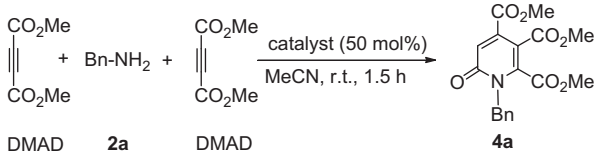
The last decade has witnessed significant advances in the use of small organic molecules to catalyze chemical transformations,[1–3] and organocatalytic methods have emerged as a powerful approach for the preparation of important building blocks or compounds.[4–7] In this Letter, we report a novel three-component reaction for the synthesis of highly functionalized 2-pyridones using *N*-methylimidazole as an organocatalyst.

The 2-pyridone moiety is found in a large number of pharmaceuticals, agrochemicals, and functional materials.[8,9] It is also a versatile synthon that can act as a common intermediate for the preparation of a wide variety of alkaloids.[9–11] Thus, the development of efficient synthetic methods for heterocycles of this type has become important in synthetic and medicinal chemistry. Recent interest in the 2-pyridone ring system has led to several new procedures for its preparation.[11–21]

In our initial investigations on the preparation of 2-pyridones, we examined the reaction between benzylamine (**2a**, 1 mmol), and dimethyl acetylenedicarboxylate (DMAD, 2 mmol) in the presence of *N*-methylimidazole (0.5 mmol). The reaction proceeded smoothly to give trimethyl 1-benzyl-6-oxo-1,6-dihydro-2,3,4-pyridinetricarboxylate (**4a**) in 80% yield (Table 1, entry 2). 1,4-Diazabicyclo[2.2.2]octane (DABCO), pyridine, and isoquinoline were found to be less effective catalysts than *N*-methylimidazole under identical reaction conditions (Table 1, entries 3–5). Other catalysts, such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), PPh_3, and K_2CO_3 were unsuccessful (Table 1, entries 6–8). Thus, *N*-methylimidazole was used as the catalyst for further studies.

A variety of different reaction conditions were employed in an attempt to optimize the yields and improve the purity of the products. First, the reaction was carried out using various amounts of the catalyst; 5 mol % of *N*-methylimidazole in MeCN was found

Table 1
Reaction of benzylamine (**2a**) with DMAD in the presence of various organocatalysts in MeCN[a]



Entry	Catalyst	Yield[b] (%)
1	None	–
2	*N*-Methylimidazole	80
3	DABCO	71
4	Pyridine	57
5	Isoquinoline	32
6	DBU	–
7	PPh_3	–
8	K_2CO_3	–

[a] Reaction conditions: **2a** (1 mmol), DMAD (2 mmol), catalyst (0.5 mmol), MeCN (5 mL).
[b] Yield of isolated pure product after column chromatography.

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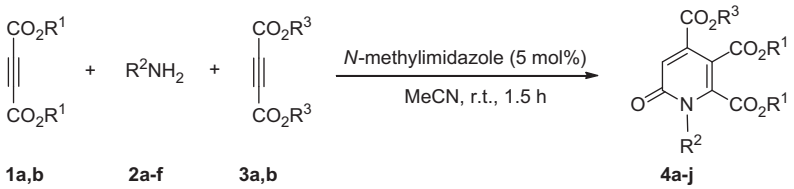
doi:10.1016/j.tetlet.2011.10.029

Table 2
Synthesis of compounds **4a–j** under the optimized reaction conditions[a]



1a,b **2a-f** **3a,b** **4a-j**

Acetylenic ester R^1		Amine R^2		Acetylenic ester R^3		Product	Yield[b] (%)
1a	Me	**2a**	Bn	**3a**	Me	**4a**	80
1a	Me	**2b**	4-MeC6H4CH2	**3a**	Me	**4b**	78
1a	Me	**2c**	4-MeOC6H4CH	**3a**	Me	**4c**	87
1a	Me	**2d**	2-ClC6H4CH2	**3a**	Me	**4d**	78
1a	Me	**2e**	4-MeOC6H4	**3a**	Me	**4e**	85
1a	Me	**2f**	*n*-Bu	**3a**	Me	**4f**	75
1b	Et	**2a**	Bn	**3b**	Et	**4g**	68
1b	Et	**2b**	4-MeOC6H4CH	**3b**	Et	**4h**	72
1a	Me	**2a**	Bn	**3b**	Et	**4i**	74
1b	Et	**2a**	Bn	**3a**	Me	**4j**	77

[a] Reaction conditions: primary alkylamine **2** (1 mmol), acetylenic ester **1** and **3** (1 mmol), *N*-methylimidazole (5 mol %), MeCN (5 mL).
[b] Yield of isolated pure compound after column chromatography.

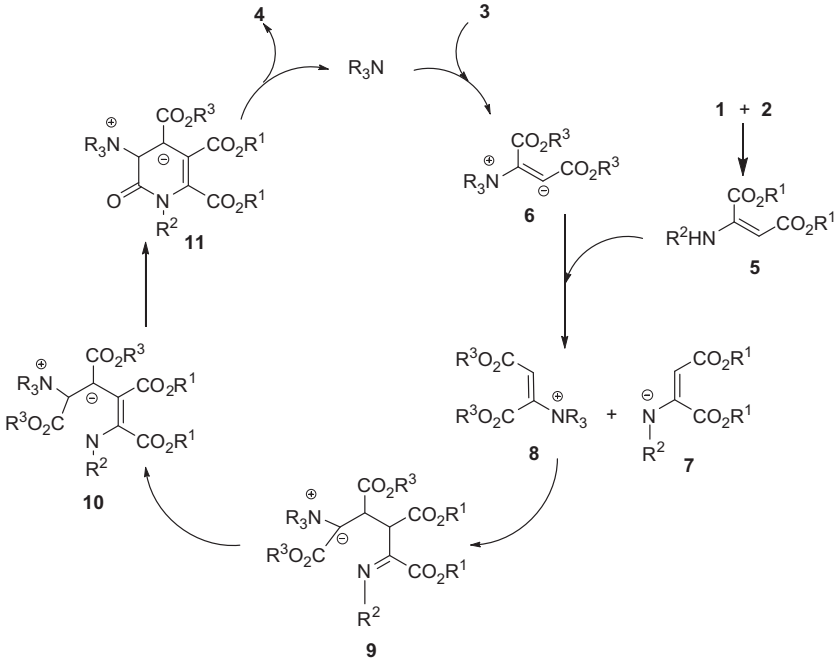
to give the best result. Subsequently, the solvent effects were examined, and the best results were obtained in MeCN.

The generality of this transformation was demonstrated by applying various primary amines and acetylenic esters under optimized conditions and the results are shown in Table 2.[22]

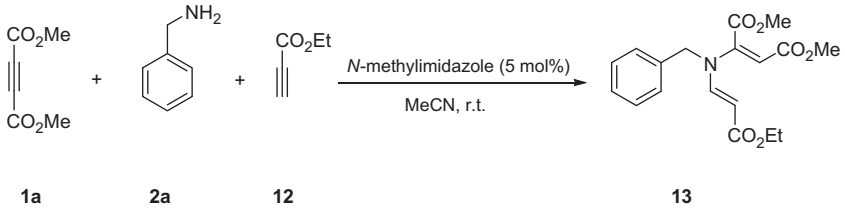
The reaction of primary amines **2** and acetylenic esters **1a,b** in the presence of *N*-methylimidazole proceeded smoothly in MeCN at rt to afford trialkyl 1-[alkyl(aryl)amino]-6-oxo-1,6-dihydro-2,3,4-pyridinetricarboxylates **4a–h** in good yields (Table 2). A wide range of structurally varied primary amines were employed in this reaction. Addition of an equimolar amount of **2** and the first acetylenic ester **1** to a 1:1 mixture of *N*-methylimidazole and the second acetylenic ester **3** in MeCN, produced 2,3-dialkyl 4-alkyl 1-1-(alkyl(aryl)amino)-6-oxo-1,6-dihydro-2,3,4-pyridinetricarboxylates **4i,j**.[23]

The structures of compounds **4a–j** were deduced from their IR, ^{1}H NMR and ^{13}C NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at the appropriate *m/z* values. The ^{1}H and ^{13}C NMR spectroscopic data, as well as IR spectra, were in agreement with the proposed structures. For example, the ^{1}H NMR spectrum of **4a** in $CDCl_3$ exhibited five sharp singlets readily recognized as arising from methoxy (δ = 3.69, 3.78 and 3.89), methylene (δ = 5.29), and vinyl (δ = 6.85) protons along with characteristic resonances for the phenyl group. The ^{1}H-decoupled ^{13}C NMR spectrum of **4a** exhibited 16 signals in agreement with the proposed structure. The ^{1}H NMR and ^{13}C NMR spectra of products **4b–j** were similar to those for **4a**, except for the patterns represented by the alkyl and aryl groups.

Presumably, the zwitterionic intermediate **6**, formed from *N*-methylimidazole (R_3N) and acetylenic ester **3**, is protonated by



Scheme 1. A plausible mechanism for the formation of compounds **4**.



Scheme 2. Synthesis of compound **13**.

the enamino ester **5**, generated in situ from primary amine **2** and acetylenic ester **1**, to produce intermediates **7** and **8** (Scheme 1). Nucleophilic attack of the conjugate base **7** on intermediate **8** leads to adduct **9**, which undergoes two proton shifts to afford new zwitterionic intermediate **10**. Finally, intramolecular cyclization affords **11**, which is converted into **4** by elimination of *N*-methylimidazole.

To extend the scope of this reaction, ethyl propiolate (**12**) was used instead of **3**. Surprisingly, the expected tandem reaction was not observed, and instead, dimethyl 2-{*N*-[(*E*)-2-(ethoxycarbonyl)vinyl]-*N*-benzylamino}maleate (**13**) was obtained in 65% yield (Scheme 2).

Formation of **13** is probably the result of the lower electrophilicity of **12** compared to **3**. The expected reaction did not proceed in the presence of pyridine or *N*-methylimidazole as catalyst. The reverse reaction was unsuccessful.

In summary, we have developed a simple, one-pot synthesis of highly functionalized 2-pyridones from reactions of primary amines with acetylenic esters in the presence *N*-methylimidazole at rt. Short reaction times, readily available starting materials, and catalysts are the main advantages of this methodology.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.10.029.

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22. *General procedure for the preparation of compounds* ***4a–h***: To a stirred solution of amine **2** (2 mmol) and acetylenic ester **1** (4 mmol) in MeCN (5 mL), was added *N*-methylimidazole (0.1 mmol) at rt. After completion of the reaction [1.5 h; TLC (AcOEt/hexane 1:4) monitoring], the solvent was evaporated and the residue was purified by column chromatography [silica gel (230–400 mesh; Merck), AcOEt/hexane 1:3].
*Trimethyl 1-benzyl-6-oxo-1,6-dihydro-2,3,4-pyridinetricarboxylate(**4a**).* White powder; mp: 99–101 °C; yield: 0.57 g (80%). IR (KBr) (ν_{max}/cm^{-1}): 2942, 1718, 1443, 1267. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 3.69 (3H, s, MeO), 3.78 (3H, s, MeO), 3.89 (3H, s, MeO), 5.29 (2H, s, CH_2N), 6.85 (1H, s, CH), 7.18 (2H, d, ^3J = 6.9 Hz, CH), 7.28–7.32 (3H, m, CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 49.0 (CH_2N), 52.8 (MeO), 53.1 (MeO), 53.3 (MeO), 108.1 (C), 121.2 (CH), 127.6 (2 CH), 128.7 (CH), 128.6 (2 CH), 134.9 (C), 142.3 (C), 144.4 (C), 160.6 (C=O), 162.0 (C=O), 163.8 (C=O), 165.5 (C=O). MS: *m*/*z* (%) = 360 (M^++1, 4), 359 (M^+, 17), 344 (4), 328 (11), 300 (65), 272 (18), 91 (25), 77 (13), 59 (5). Anal. Calcd for $C_{18}H_{17}NO_7$ (359.33): C, 60.17; H, 4.77; N, 3.90. Found: C, 60.39; H, 4.82; N, 3.81.
*Triethyl 1-benzyl-6-oxo-1,6-dihydro-2,3,4-pyridinetricarboxylate (**4g**).* Yellow oil; yield: 0.55 g (68%). IR (KBr) (ν_{max}/cm^{-1}): 2945, 1725, 1435, 1251. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.07 (3H, t, ^3J = 7.2 Hz, Me), 1.28 (3H, t, ^3J = 7.1 Hz, Me), 1.38 (3H, t, ^3J = 7.2 Hz, Me), 4.15 (2H, q, ^3J = 7.2 Hz, CH_2O), 4.23 (2H, q, ^3J = 7.1 Hz, CH_2O), 4.35 (2H, q, ^3J = 7.2 Hz, CH_2O), 5.31 (2H, s, CH_2N), 6.84 (1H, s, CH), 7.18 (2H, d, ^3J = 7.1 Hz, CH), 7.25-7.35 (3H, m, CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 14.1 (Me), 14.8 (Me), 14.9 (Me), 51.0 (CH_2N), 63.0 (CH_2O), 63.2 (CH_2O), 63.9 (CH_2O), 109.2 (C), 128.3 (2 CH), 128.8 (CH), 129.5 (2 CH), 135.9 (C), 139.9 (C), 143.7 (C), 145.6 (C), 161.7 (C=O), 162.6 (C=O), 164.4 (C=O), 166.1 (C=O). MS: *m*/*z* (%) = 402 (M^++1, 5), 401 (M^+, 21), 372 (5), 356 (25), 328 (73), 300 (27), 91 (35), 77 (29), 73 (15). Anal. Calcd for $C_{21}H_{23}NO_7$ (401.41): C, 62.84; H, 5.78; N, 3.49. Found: C, 63.20; H, 5.70; N, 3.55.
23. *General procedure for the preparation of compounds* ***4i,j***: To a stirred solution of amine **2a** (2 mmol) and the first acetylenic ester **1** (2 mmol) in MeCN (5 mL), was added *N*-methylimidazole (0.1 mmol) and the second acetylenic ester **3** (2 mmol) at rt. After completion of the reaction [1.5 h; TLC (AcOEt/hexane 1:4) monitoring], the solvent was evaporated and the residue was purified by column chromatography [silica gel (230–400 mesh; Merck), AcOEt/hexane 1:3].
*4-Ethyl 2,3-dimethyl 1-benzyl-6-oxo-1,6-dihydro-2,3,4-pyridinetricarboxylate (**4i**).* White powder; mp: 84–86 °C; yield: 0.55 g (74%). IR (KBr) (ν_{max}/cm^{-1}): 2958, 1736, 1677, 1445, 1276. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.35 (3H, t, ^3J = 7.1 Hz, Me), 3.69 (3H, s, MeO), 3.77 (3H, s, MeO), 4.35 (2H, q, ^3J = 7.1 Hz, CH_2O), 5.30 (2H, s, CH_2N), 6.85 (1H, s, CH), 7.19 (2H, d, ^3J = 7.1 Hz, CH), 7.26-7.32 (3H, m, CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 14.0 (Me), 49.0 (CH_2N), 52.7 (MeO), 53.3 (MeO), 62.4 (CH_2O), 108.3 (C), 121.2 (CH), 127.5 (2CH), 128.0 (CH), 128.6 (2CH), 140.0 (C), 142.5 (C), 144.3 (C), 160.7 (C=O), 162.1 (C=O), 163.9 (C=O), 165.0 (C=O). MS: *m*/*z* (%) = 374 (M^++1, 11), 373 (M^+, 53), 358 (4), 342 (26), 328 (7), 314 (61), 286 (16), 91 (32), 77 (27), 59 (8). Anal. Calcd for $C_{19}H_{19}NO_7$ (373.36): C, 61.12; H, 5.13; N, 3.75. Found: C, 60.79; H, 5.20; N, 3.83.
*Dimethyl 2-{benzyl[(E)-3-ethoxy-3-oxo-1-propenyl]amino}-2-butenedioate (**13**).* White powder; mp: 96–98 °C; yield: 0.45 g (65%). IR (KBr) (ν_{max}/cm^{-1}): 2955, 1712, 1463, 1255. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.24 (3H, t, ^3J = 7.0 Hz, Me), 3.66 (3H, s, MeO), 4.00 (3H, s, MeO), 4.14 (2H, q, ^3J = 7.0 Hz, OCH_2), 4.66 (2H, s, CH_2N), 5.17 (1H, d, ^3J = 13.4 Hz, CH), 5.23 (1H, s, CH), 7.15 (2H, d, ^3J = 7.6 Hz, CH), 7.29 (2H, t, ^3J = 7.1 Hz, CH), 7.36 (1H, t, ^3J = 7.4 Hz, CH), 7.61 (1H, d, ^3J = 13.4 Hz, CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 14.2 (Me), 51.2 (CH_2N), 51.9 (MeO), 53.5 (MeO), 60.1 (OCH_2), 96.9 (CH), 99.1 (CH), 125.7 (2 CH), 127.9 (CH), 129.1 (2 CH), 133.0 (C), 163.3 (CH), 150.1 (C), 164.4 (C=O), 166.3 (C=O), 167.0 (C=O). MS: *m*/*z* (%) = 347 (M^+, 3), 332 (8), 288 (11), 91 (25), 77 (13), 59 (5). Anal. Calcd for $C_{18}H_{21}NO_6$ (347.36): C, 62.24; H, 6.09; N, 4.03. Found: C, 61.93; H, 6.14; N, 4.11.