β-Nitroacrylates as Precursors of Tetrasubstituted Furans in a One-Pot Process and under Acidic Solvent-Free Conditions

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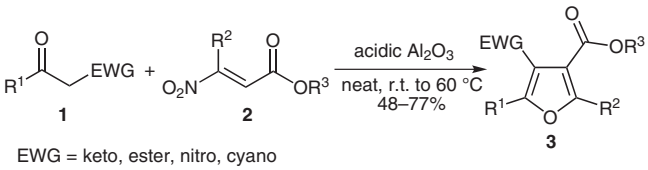
Abstract: The reaction of α-functionalized carbonyl derivatives with β-nitroacrylates, catalyzed by acidic alumina and in the absence of solvent, allows the one-pot synthesis of tetrasubstituted furan derivatives, in which at least two powerful functionalities are present in the 3- and 4-positions.

Key words: heterocycles, heterogeneous catalysis, furans, β-nitroacrylates, domino reaction



Scheme 1

Highly substituted furans are found as key structural elements in many bioactive natural products and important pharmaceuticals.[1] They also represent versatile building blocks for the synthesis of more elaborate heterocyclic compounds.[2] On this basis, a large number of synthetic methods to approach substituted furans have been developed[3] and, among them, the Paal–Knorr (from 1,4-dicarbonyl derivatives)[4] and the Feist–Benary syntheses[5] are the most popular.

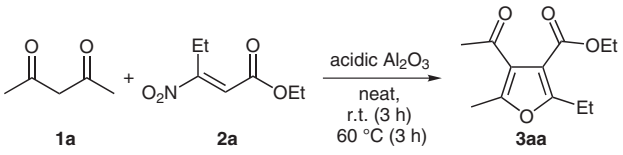
Although these methods have proved to be very useful for the synthesis of furan derivatives, there are some limitations, including the difficulty to access furans with sensitive functional groups, as well as limitations in flexibility regarding their substitution pattern. Furan derivatives have been prepared from β-nitroalkenes by initial Michael addition reaction with 1,3-dicarbonyl compounds, under basic conditions.[6] Even though this approach permits the access to polysubstituted furans, it requires problematic solvents (xylene, 1,2-dimethoxyethane, or dimethyl sulfoxide) and seems to be constrained to a restricted variety of substrates. Recently, the usefulness of conjugated nitroalkenes as co-reactants with 1,3-dicarbonyl derivatives has been highlighted in the synthesis of specific arylbenzofurans under homogeneous conditions.[7,8]

In this context, in a development of our earlier studies to Michael addition of substrates containing active methylene groups to nitroalkenes,[9] we have investigated the reactivity of β-nitroacrylates with α-functionalized carbonyl derivatives in order to obtain new classes of polyfunctionalized furans under mild conditions (Scheme 1).

β-Nitroacrylates are a highly reactive class of doubly activated olefins having two electron-withdrawing groups in both α- and β-positions, and this particular molecular framework makes them useful starting materials for the synthesis of important targets, such as both aliphatic and aromatic heterocycles,[10] α,β-unsaturated esters[11] and α- or β-keto esters.[11a,12]

Based on our experience, and due to the ready enolization of substrates **1**, we began the optimization studies of the reaction under acidic conditions. Furthermore, in order to avoid the presence of any solvent, we focused our attention on solid acids. Thus, we investigated a range of solid promoters (acidic alumina, Montmorillonite K-10, and zeolite HSZ-320), under neat conditions, using the reaction of **1a** with **2a** as model, and we found acidic alumina to be the most effective. Subsequently, we tested a variety of substrate/promoter ratios (r.t. for 3 h than heating at 60 °C for 3 h) and, as shown in Table 1, the optimal result was obtained using an alumina/substrate ratio of 1.2 g/mmol.

Table 1 Synthesis of **3aa** with a Variety of Substrate/Promoter Ratios



1a **2a** **3aa**

Ratio of acidic Al_2O_3/substrate	Yield (%)[a] of **3aa**
3.0 g/mmol	68
1.5 g/mmol	70
1.2 g/mmol	77
1.0 g/mmol	66

[a] Yield of pure isolated product.

Encouraged by these results, and in order to assess the generality of our method, a number of different α-functionalized carbonyl derivatives **1** and β-nitroacrylates **2** was tested. As shown in Table 2, the reactions proceeded in satisfactory to good overall yields (48–77%).

It is important to note that tetrasubstituted furans **3** obtained by this protocol possess at least two functionalities,

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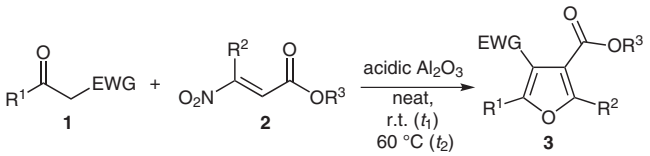
Table 2 Synthesis of Compounds **3**[13]



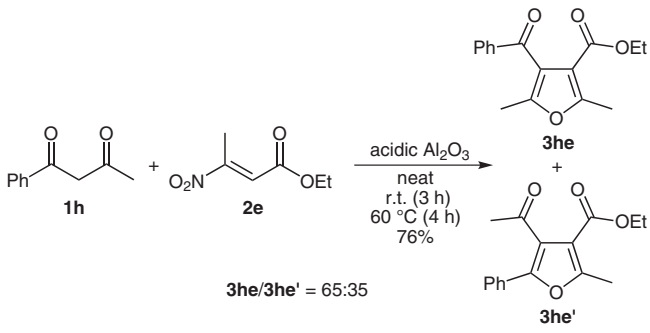
Ketone			β-Nitroacrylate			Product	Yield	Time (h)
1	R^1	EWG	**2**	R^2	R^3	**3**	(%)[a]	$t_1 + t_2$
1a	Me	C(O)Me	**2a**	Et	Et	**3aa**	77	3 + 3
1a	Me	C(O)Me	**2b**	$Me_2CH(CH_2)_2$	Et	**3ab**	70	3 + 3
1a	Me	C(O)Me	**2c**	$Me(CH_2)_4$	Et	**3ac**	72	3 + 3
1b	Me	CO_2Et	**2a**	Et	Et	**3ba**	56	4 + 15
1c	Pr	CO_2Et	**2d**	$Ph(CH_2)_2$	Et	**3cd**	48	4 + 24
1d	$-(CH_2)_3C(O)-$		**2e**	Me	Et	**3de**	75	3 + 3
1d	$-(CH_2)_3C(O)-$		**2f**	Bu	Et	**3df**	76	3 + 3
1e	Et	C(O)Et	**2g**	$Me(CH_2)_4$	Bu	**3eg**	58	3.5 + 6
1e	Et	C(O)Et	**2c**	$Me(CH_2)_4$	Et	**3ec**	57	3.5 + 8
1f	Ph	NO_2	**2a**	Et	Et	**3fa**	49	3 + 3
1g	$-CH_2C(Me)_2CH_2C(O)-$		**2h**	$MeO_2C(CH_2)_4$	Et	**3gh**	50	3.5 + 5
1h	Ph	CN	**2c**	$Me(CH_2)_4$	Et	**3hc**	49	3 + 3

[a] Yield of pure isolated product.

such as keto, ester, nitro, and cyano groups in the 3- and 4-positions. Such functionalities, whilst very useful for subsequent transformations, are difficult to introduce by other approaches. In addition, by the appropriate choice of the alkyl groups (R^1 and R^2) in the starting material **1** and **2**, it is possible to introduce a variety of substituents at the 2- and 5-positions.

Regarding the regioselectivity of the procedure; by using nonsymmetrical ketones, we tested the reaction of **1h** with **2e** (Scheme 2) and, although the reaction works with good overall yield (76%), the regioselectivity is moderate, and we isolated the regioisomeric products **3he** and **3he′** in 65:35 ratio.

In conclusion, considering that this procedure works well in the absence of any solvent and affords compounds **3** without the need for any quenching or extraction as the reaction mixture can be directly charged into a chromatography column for immediate purification, our method can be considered to be simple, mild, and possessing generality.



Scheme 2

Acknowledgment

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(13) **Typical Procedure for the Synthesis of Compounds 3**
To a stirred mixture of the active methylene derivative **1** (1 mmol) and β-nitroacrylate **2** (1 mmol), acidic alumina (1.2 g) was added. The resulting heterogeneous mixture was initially stirred at r.t., then heated at 60 °C, and stirred for the appropriate time (see Table 2; reaction progress was monitored by TLC). After completion of the reaction the cooled heterogeneous system was directly charged onto a silica gel column (eluting with hexanes–EtOAc) to give the pure product **3**.

Spectroscopic Data for Representative Compounds.

Compound **3aa**: clear oil. IR (neat): ν = 1050, 1189, 1301, 1577, 1684, 1716 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.21 (t, 3 H, *J* = 7.7 Hz), 1.32 (t, 3 H, *J* = 7.3 Hz), 2.35 (s, 3 H), 2.40 (s, 3 H), 2.86 (q, 2 H, *J* = 7.7 Hz), 4.29 (q, 2 H, *J* = 7.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.6, 13.2, 14.4, 21.2, 31.2, 60.9, 112.1, 123.0, 153.7, 161.8, 163.8, 197.3. MS (EI, 70 eV): *m/z* = 224 [M^+], 181, 178 (100), 163, 135, 122, 108, 57, 43, 29. Anal. Calcd for $C_{12}H_{16}O_4$ (224.25): C, 64.27; H, 7.19. Found: C, 64.34; H, 7.23.

Compound **3ba**: clear oil. IR (neat): ν = 1097, 1210, 1589, 1719 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.21 (t, 3 H, *J* = 7.7 Hz), 1.31 (t, 6 H, *J* = 7.3 Hz), 2.43 (s, 3 H), 2.80 (q, 2 H, *J* = 7.7 Hz), 4.27 (q, 4 H, *J* = 7.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.6, 13.3, 14.3, 14.4, 20.8, 60.7, 60.8, 113.1, 113.8, 155.7, 160.2, 163.9. MS (EI, 70eV): *m/z* = 254 [M^+], 208 (100), 180, 152, 108, 43. Anal. Calcd for $C_{13}H_{18}O_4$ (254.28): C, 61.40; H, 7.14. Found: C, 61.51; H, 7.19.

Compound **3de**: clear oil. IR (neat): ν = 1046, 1190, 1582, 1687, 1735 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.36 (t, 3 H, *J* = 7.3 Hz), 2.08–2.17 (m, 2 H), 2.46–2.51 (m, 2 H), 2.48 (s, 3 H), 2.82 (t, 2 H, *J* = 6.4 Hz), 4.32 (q, 2 H, *J* = 7.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.5, 14.4, 22.4, 23.6, 38.8, 60.9, 111.9, 119.6, 158.5, 163.6, 165.8, 192.2. MS (EI, 70 eV): *m/z* = 222 [M^+], 194, 176 (100), 166, 138, 78, 43. Anal. Calcd for $C_{12}H_{14}O_4$ (222.24): C, 64.85; H, 6.35. Found: C, 64.94; H, 6.41.

Compound **3gh**: clear oil. IR (neat): ν = 1223, 1583, 1689, 1736 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.11 (s, 6 H), 1.35 (t, 3 H, *J* = 7.3 Hz), 1.60–1.74 (m, 4 H), 2.32 (t, 2 H, *J* = 6.8 Hz), 2.38 (s, 2 H), 2.69 (s, 2 H), 2.89 (t, 2 H, *J* = 6.8 Hz), 3.64 (s, 3 H), 4.31 (q, 2 H, *J* = 7.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3, 24.5, 27.1, 27.6, 28.6, 33.8, 35.1, 37.5, 53.3, 61.0, 111.7, 118.4, 162.1, 163.5, 165.0, 174.0, 191.9. MS (EI, 70eV): *m/z* = 350 [M^+], 319, 304, 272, 244, 231, 217 (100), 55, 29. Anal. Calcd for $C_{19}H_{26}O_6$ (350.41): C, 65.13; H, 7.48. Found: C, 65.22; H, 7.56.

Compound **3hc**: clear oil. IR (neat): ν = 691, 1112, 1492, 1586, 1603, 1721, 2232, 3062 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.90 (t, 3 H, *J* = 6.8 Hz), 1.31–1.39 (m, 4 H), 1.41 (t, 3 H, *J* = 7.3 Hz), 1.68–1.79 (m, 2 H), 3.05 (t, 2 H, *J* = 7.7 Hz), 4.38 (q, 2 H, *J* = 7.3 Hz), 7.40–7.50 (m, 3 H), 7.98 (d, 2 H, *J* = 7.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 14.2, 22.4, 27.6, 27.7, 31.4, 61.3, 92.1, 114.2, 114.5, 125.7, 127.7, 129.2, 130.5, 158.7, 161.8, 163.3. MS (EI, 70eV): *m/z* = 311 [M^+], 282, 254, 226 (100), 105, 77, 29. Anal. Calcd for $C_{19}H_{21}NO_3$ (311.37): C, 73.29; H, 6.80; N, 4.50. Found: C, 73.33; H, 6.85; N, 4.46.