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The Aldol Addition of Readily Enolizable 1,3-Dicarbonyl Compounds to 2-Cyanobenzaldehyde in the Synthesis of Novel 3-Substituted Isoindolinones

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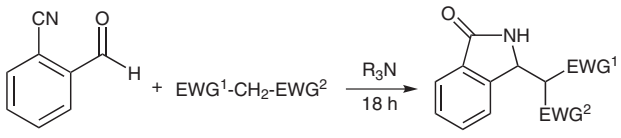
Abstract: The aldol addition of readily enolizable 1,3-dicarbonyl compounds to 2-cyanobenzaldehyde in the presence of a tertiary amine led to a series of new 3-substituted isoindolinones. Despite the instability of the related aldols, this synthesis was possible because of the intramolecular trapping of the adducts with the cyano group due to a tandem process of cyclization and rearrangement. Simple decarboxylation of some derivatives gave access to very useful compounds.

Key words: isoindolinones, aldol addition, enolizable 1,3-dicarbonyl compounds, 2-cyanobenzaldehyde

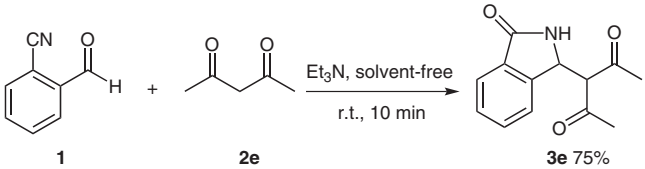
In the last few years the chemistry of isoindolinones has attracted much attention due to their large number of applications in therapeutic activities,[1] and also their presence in many naturally occurring substances.[2] Consequently, considerable effort has been devoted to the synthesis of structurally different derivatives, both chiral and racemic.[1,3,4] Many methods are available, but they often require multistep, inflexible strategies for the construction of the heterocyclic ring.[1,3] For these reasons great attention is still devoted to the development of new, simple methods for the construction of isoindolinone rings. In this context, Ramström et al. have very recently proposed a useful one-pot tandem nitroaldol–cyclization–rearrangement reaction for the synthesis of 3-substituted isoindolinones by reaction of 2-cyanobenzaldehyde with nitroalkanes in the presence of tertiary base.[4] Since this process was possible thanks to the relatively acidic α protons of nitro compounds, our idea is related to the development of a more general approach which exploits the aldol addition of readily enolizable 1,3-dicarbonyl compounds to 2-cyanobenzaldehyde. However, it is important to note that the aldol addition of readily enolizable 1,3-dicarbonyl compounds, such as β-keto esters and malonates, to aldehydes is very difficult to achieve, and very few applications are available, whereas the nitroaldol (Henry reaction) is a well-established procedure. We recently demonstrated that trapping of these unstable aldol adducts in the presence of chlorosilane reagents is a straightforward strategy to drive these difficult aldol additions to completion.[5] Thus, based on this concept, the intramolecular trapping of the intermediate aldol adducts by irreversible cyclization at the cyano group would allow the synthesis of different types of 3-substituted isoindolinones.

On the basis of these considerations, according to Scheme 1, a series of readily enolizable 1,3-dicarbonyl compounds **2** reacted with 2-cyanobenzaldehyde (**1**) in the presence of triethylamine, and the results are reported in Table 1.



Scheme 1

Under optimized conditions we were pleased to observed that all the model nucleophiles, representing the classes of malonates, β-keto esters, and 1,3-diketones, gave the new 3-substituted isoindolinones **3** in good to high yields, however, only acetylacetone, under the same conditions, showed significantly lower reactivity (Table 1, entry 5). However, a good yield was observed in a very short time when it was reacted under solvent-free conditions (Scheme 2).



Scheme 2

It is worthy of note that the obtained isoindolinones **3** show very interesting functionalities and they could be very useful for further transformations in the synthesis of valuable compounds. For example, according to Scheme 3, the decarboxylation of the β-keto ester derivative **3b**, by employing a modification of the mild Krapcho procedure[6] led to known compound **4**, previously obtained from by less effective synthesis employing a cobalt(II) catalyst.[3b]

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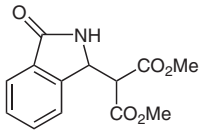
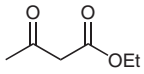
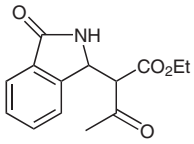
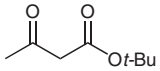
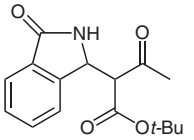
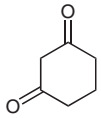
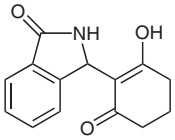
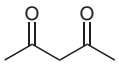
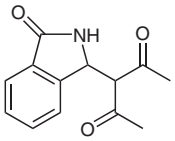
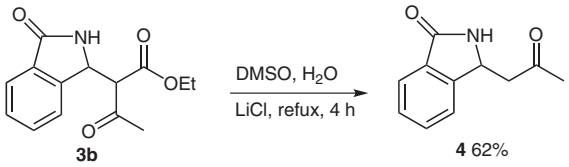
Table 1 Synthesized 3-Substitued Isoindolinones **3**

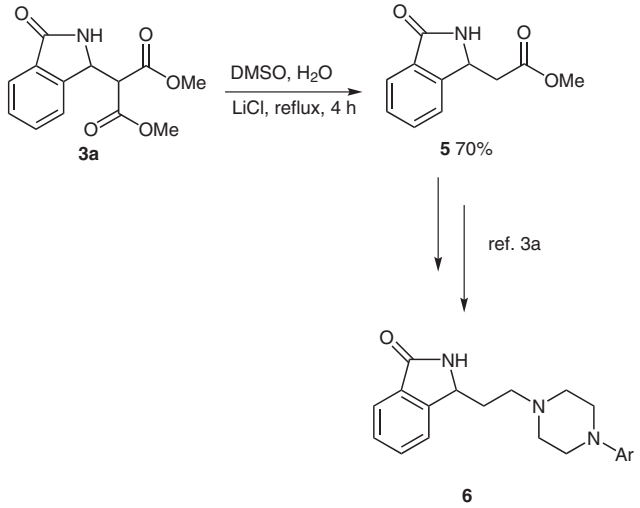
Entry	2	Adduct 3	Yield[a] (%)	
1	**2a**	$CH_2(CO_2Me)_2$	**3a**	 87
2	**2b**		**3b**	 67 (dr 1:1)[b]
3	**2c**		**3c**	 87 (dr 1.5:1)
4	**2d**		**3d**	 64
5	**2e**		**3e**	 25

[a] Yields refer to chromatographically pure compounds.
[b] Diastereomeric ratios were calculated on the basis of ^{1}H NMR spectrum of the crude product.

The same decarboxylation procedure performed on **3a** led to the very interesting compound **5** in good yield (Scheme 4), a well-known intermediate in the synthesis of a series of achiral and chiral piperazine derivatives **6** for dopamine D_4 receptor, a good target for the treatment of schizophrenia, that otherwise required a longer and more tedious method of synthesis.[3a]

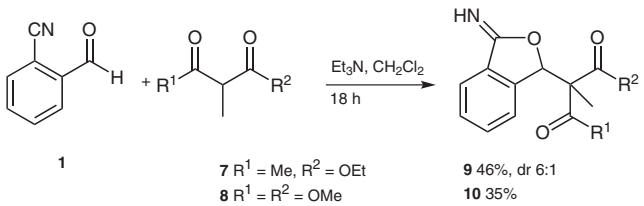


Scheme 3



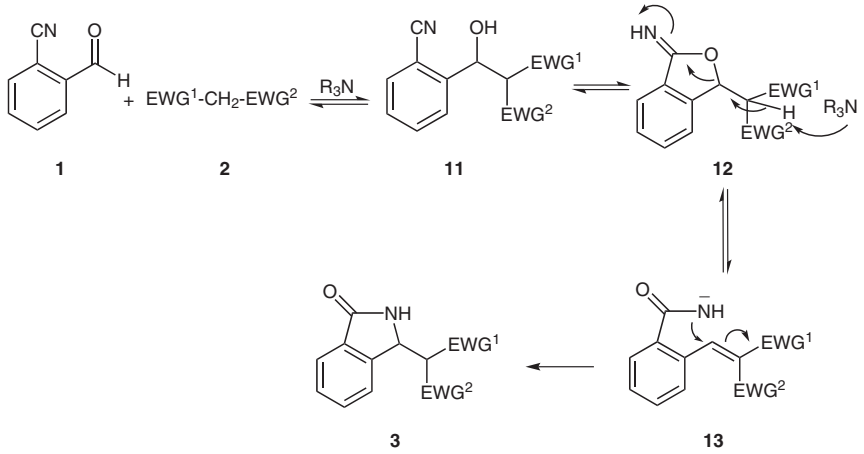
Scheme 4

As reported by Ramström, the presence of two acidic protons in the α-position of nitroalkanes is the fundamental requisite that allows the isoindolinone ring to be obtained.[4] In fact, when ethyl 2-methylacetoacetate (**7**) or dimethyl methylmalonate (**8**) were reacted under the conditions of Scheme 1, new products were obtained in significantly lower yields. The structure of these compounds was attributed to the iminoisobenzofurans **9** and **10**, respectively, by comparison with spectroscopic data of reported analogues (Scheme 5).[4,7]



Scheme 5

Thus, on the basis of the obtained results, a general pathway can reasonably be proposed for the series of readily enolizable 1,3-dicarbonyl compounds (Scheme 6). After the reversible deprotonation of **2** and its subsequent nu-



Scheme 6

cleophilic addition to the aldehyde **1**, the unstable adduct **11** gives the iminoisobenzofuran **12** by cyclization at the cyano group. Deprotonation of **12** in the presence of a base and rearrangement gives the acyclic intermediate **13**. Finally, the intramolecular conjugated addition of **13** leads to the title isoindolinones **3**.

In conclusion, a study of the aldol addition of readily enolizable 1,3-dicarbonyl compounds to 2-cyanobenzaldehyde gave us the possibility to develop a simple and general access to a series of new 3-substituted isoindolinones in the presence of tertiary amines under very mild conditions. Because of the simplicity of the method and the importance of the obtained products, other studies are in course in our group so as to further expand the scope and develop asymmetric versions in the presence of chiral tertiary amines.

All reactions were performed in oven-dried (140 °C) or flame-dried glassware under dry N_2. CH_2Cl_2 was reagent grade and was dried and distilled immediately from CaH_2 before use. Column chromatographic purification of products was carried out using silica gel 60 (70–230 mesh, Merck). The reagents (Aldrich and Fluka) were used without further purification. The NMR spectra were recorded on Bruker DRX 400, 300, 250 spectrometers [400 MHz, 300 MHz, 250 MHz (^{1}H); 100 MHz, 75 MHz, 62.5 MHz (^{13}C)]. Spectra were referenced to residual $CHCl_3$ [δ = 7.26 (^{1}H), 77.23 (^{13}C)]. Yields are given for isolated products showing one spot on a TLC plate and no impurities detectable in the NMR spectrum. Mass spectral analyses were carried out using an electrospray spectrometer, Waters 4 micro quadrupole. Elemental analyses were performed with FLASHEA 1112 series-Thermo Scientific for CHNS-O apparatus.

2,3-Dihydro-1*H*-isoindol-1-ones 3; General Procedure

2-Cyanobenzaldehyde (**1**, 0.40 mmol) was added to a soln of 1,3-dicarbonyl compound **2** (0.44 mmol) and Et_3N (0.40 mmol) in CH_2Cl_2 (2.0 mL). At the end of the reaction (TLC monitoring), the mixture was diluted with EtOAc (2 mL) and the solvent evaporated under reduced pressure. Then the crude product was purified by flash chromatography (hexane–EtOAc, 8:2 to 1:1) to afford pure **3**.

Dimethyl 2-(3-Oxo-2,3-dihydro-1*H*-isoindol-1-yl)malonate (3a)

Solid; yield: 91 mg (87%); mp 154–155 °C.

IR (KBr): 3182, 3051, 1742, 1696, 1434, 1263, 1143, 965, 769, 751 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 7.5 Hz, 1 H), 7.53–7.47 (m, 2 H), 7.32 (m, 2 H), 5.18 (d, *J* = 7.5 Hz, 1 H), 3.81 (s, 3 H), 3.67 (s, 3 H), 3.62 (d, *J* = 7.5 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.3, 168.8, 168.3, 144.9, 133.3, 133.2, 130.2, 125.3, 124.1, 57.1, 56.1, 54.3, 53.2.

MS (ESI): *m*/*z* = 286 [M + Na$^+$].

Anal. Calcd for $C_{13}H_{13}NO_5$: C, 59.31; H, 4.98; N, 5.32. Found: 59.45; H, 5.04; N, 5.15.

Ethyl 3-Oxo-2-(3-oxo-2,3-dihydro-1*H*-isoindol-1-yl)butanoate (3b)

Solid; yield: 70 mg (67%); mixture of diastereoisomers.

IR (KBr): 3237, 2982, 2925, 2854, 1701, 1616, 1470, 1359, 1308, 1204, 1096, 1017, 751, 695 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 6.60 Hz, 2 H), 7.54–7.46 (m, 4 H), 7.34–7.26 (m, 2 H), 6.86–6.83 (m, 2 H), 5.24 (d, *J* = 8.02 Hz, 2 H), 4.36–4.27 (q, 2 H), 4.16–4.08 (q, 2 H), 3.81 (d, *J* = 7.65 Hz, 1 H), 3.65 (d, *J* = 8.37 Hz, 1 H), 2.34 (s, 3 H), 2.18 (s, 3 H), 1.34–1.28 (t, 3 H), 1.15–1.10 (t, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.9, 201.9, 171.0, 170.9, 168.4, 167.8, 145.4, 145.4, 133.3, 133.3, 133.2, 130.2, 130.1, 125.5, 125.4, 124.1, 65.4, 64.1, 63.5, 63.4, 55.7, 55.6, 32.4, 30.9, 15.2, 15.0.

MS (ESI): *m*/*z* = 284 [M + Na$^+$].

Anal. Calcd for $C_{14}H_{15}NO_4$: C, 66.36; H, 5.79; N, 5.36. Found: C, 66.47; H, 5.65; N, 5.43.

***tert*-Butyl 3-Oxo-2-(3-oxo-2,3-dihydro-1*H*-isoindol-1-yl)butanoate (3c)**

Solid; yield: 101 mg (87%); mixture of diastereomers.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.86 (br d, *J* = 6.0 Hz, 1 + 1 H), 7.56–7.49 (m, 3 + 2 H), 7.31 (d, *J* = 6.0 Hz, 1 H), 7.12 (br s, 1 H), 6.68 (br s, 1 H), 5.18 (d, *J* = 8.0 Hz, 1 H), 5.14 (d, *J* = 6.0 Hz, 1 H), 3.78 (d, *J* = 6.0 Hz, 1 H), 3.60 (d, *J* = 8.0 Hz, 1 H), 2.35 (s, 3 H), 2.17 (s, 3 H), 1.42 (s, 9 H), 1.29 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.3, 201.1, 169.9, 169.8, 166.1, 165.5, 144.4, 144.3, 132.1, 132.0, 131.9, 131.8, 128.7, 128.6, 123.9, 123.3, 122.8, 83.4, 83.3, 64.8, 63.3, 54.5, 54.4, 30.7, 29.5, 27.7, 27.5.

MS (ESI): *m*/*z* = 290 [M + H$^+$].

Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.35; H, 6.53; N, 4.90.

2-(3-Oxo-2,3-dihydro-1*H*-isoindol-1-yl)cyclohexane-1,3-dione (3d)
Solid; yield: 63 mg (65%); mp 210 °C (dec).

IR (KBr): 3286, 2931, 1631, 1389, 1302, 995, 683 cm^{-1}.

^1H NMR (400 MHz, CD_3OD): δ = 7.71 (d, *J* = 8.0 Hz, 1 H), 7.50–7.46 (t, 1 H), 7.39–7.35 (t, 1 H), 7.25 (d, *J* = 8.0 Hz, 1 H), 5.96 (s, 1 H), 2.40–2.29 (m, 4 H), 1.96–1.91 (q, 2 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 191.5, 173.7, 150.8, 133.4, 132.4, 127.7, 123.4, 122.9, 110.5, 53.1, 35.1, 21.8.

MS (ESI): *m*/*z* = 244 [M + H^+].

Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: 69.31; H, 5.28; N, 5.67.

3-(3-Oxo-2,3-dihydro-1*H*-isoindol-1-yl)pentane-2,4-dione (3e)
Solid; yield: 70 mg (76%); mp 146.7–147.8 °C.

IR (KBr): 3226, 3081, 3025, 2919, 2849, 1697, 1417, 1358, 1311, 1238, 1138, 749, 696 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 7.81 (d, *J* = 5.0 Hz, 1 H), 7.56–7.46 (m, 4 H), 7.30 (d, *J* = 7.5 Hz, 1 H), 5.64 (s, 1 H, enol form), 5.25 (d, *J* = 5.0 Hz, 1 H), 4.06 (d, *J* = 7.5 Hz, 1 H), 2.40 (s, 3 H, enol form), 2.26 (s, 3 H), 2.08 (s, 3 H), 1.41 (s, 3 H, enol form).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.5, 202.3, 198.4, 190.6, 172.9, 171.5, 148.3, 145.4, 133.8, 133.5, 133.3, 133.2, 130.2, 129.8, 125.5, 125.2, 124.1, 123.6, 108.0, 72.3, 56.2, 32.7, 31.8, 25.6, 24.1.

MS (ESI): *m*/*z* = 254 [M + Na^+].

Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.45; H, 5.78; N, 6.12.

Decarboxylation Reaction To Give 4 or 5; General Procedure
Compound **3a** or **3b** (0.22 mmol), DMSO (4.0 mL), H_2O (0.30 mL), and LiCl (0.50 mmol) were placed in a round-bottom flask equipped with a magnetic bar and a reflux condenser. The soln was heated to refluxing using an oil bath with stirring for 4 h. After cooling to r.t., the soln was added to EtOAc (60 mL), extracted with brine (3 × 20 mL), and dried (anhyd Na_2SO_4). Then the solvent was removed under reduced pressure and the crude product was purified by chromatography (hexane–EtOAc, 8:2 to 1:1).

3-(2-Oxopropyl)-2,3-dihydro-1*H*-isoindol-1-one (4)[3b]
Solid; yield: 26 mg (62%); mp 132.7–134.1 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 7.3 Hz, 1 H), 7.65–7.36 (m, 2 H), 7.38 (d, *J* = 7.3 Hz, 1 H), 6.68 (br s, 1 H), 4.94 (br d, *J* = 7.8 Hz, 1 H), 3.21 (dd, *J* = 3.2, 18.5 Hz, 1 H), 2.59 (dd, *J* = 10.2, 18.5 Hz, 1 H), 2.24 (s, 3 H).

MS (ESI): *m*/*z* = 190 [M + H^+].

Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.62; H, 5.70; N, 7.68.

Methyl (3-Oxo-2,3-dihydro-1*H*-isoindol-1-yl)acetate (5)
Solid; yield: 32 mg (70%); mp 145.6–157.7 °C.

^1H NMR (250 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 7.1 Hz, 1 H), 7.59–7.40 (m, 3 H), 6.93 (br s, 1 H), 4.93 (dd, *J* = 10.2, 3.3 Hz, 1 H), 3.78 (s, 3 H), 3.03 (dd, *J* = 3.4, 17.1 Hz, 1 H), 2.46 (dd, *J* = 10.2, 17.2 Hz, 1 H), 2.24 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): d = 171.6, 170.0, 145.6, 132.0, 131.7, 128.6, 124.1, 122.2, 52.6, 52.2, 39.2.

MS (ESI): *m*/*z* = 206 [M + H^+].

Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.52; H, 5.30; N, 6.68.

1,3-Dihydroisobenzofuran-1-imines 9 and 10; General Procedure
2-Cyanobenzaldehyde (**1**, 46 mg, 0.40 mmol) was added to a soln of ethyl 2-methylacetoacetate (**7**, 62 μL, 0.44 mmol) or dimethyl methylmalonate (**8**, 58 μL, 0.44 mmol) and Et_3N (61 μL, 0.44 mmol) in CH_2Cl_2 (1.0 mL) at r.t. At the end of the reaction (TLC monitoring), the mixture was diluted with EtOAc (2 mL) and the solvent evaporated under reduced pressure. Then the crude was purified by flash chromatography (hexane–EtOAc, 8:2 to 1:1) to give pure **9** and **10**.

Ethyl 2-(3-Imino-1,3-dihydroisobenzofuran-1-yl)-2-methyl-3-oxobutanoate (9)
Oil; yield: 51 mg (46%); mixture of diastereomers.

IR (KBr): 3296, 2984, 1716, 1693, 1468, 1357, 1252, 1158, 1116, 1021, 984, 839, 779, 609 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 7.47 Hz, 1 H), 7.51–7.45 (m, 2 H), 7.35 (d, *J* = 6.90 Hz, 1 H), 6.26 (s, 1 H), 6.24 (s, 1 H, minor), 4.28–4.15 (m, 2 H), 2.33 (s, 3 H), 2.17 (s, 3 H, minor), 1.30–1.12 (m, 3 H), 1.09 (s, 3 H), 1.06 (s, 3 H, minor).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.5 (minor), 202.0, 169.4, 168.9 (minor), 166.7, 143.5, 143.3 (minor), 132.2, 130.4 (minor), 129.9, 129.3, 123.8, 123.7, 123.2, 83.7 (minor), 83.3, 64.3 (minor), 63.8, 62.2 (minor), 61.9, 29.5, 26.6, 26.4 (minor), 13.7 (minor), 13.6.

MS (ESI): *m*/*z* = 276 [M + H^+].

Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.53; H, 6.17; N, 5.01.

Dimethyl 2-(3-Imino-1,3-dihydroisobenzofuran-1-yl)-2-methylmalonate (10)
Oil; yield: 39 mg (35%).

IR (KBr): 3298, 2954, 1732, 1694, 1468, 1435, 1355, 1268, 1157, 1112, 1034, 978, 839, 779, 751, 662 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 7.55 (d, *J* = 5.75 Hz, 1 H), 7.53–7.41 (m, 3 H), 6.20 (s, 1 H), 3.82 (s, 3 H), 3.78 (s, 3 H), 1.13 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.59, 169.16, 166.7, 143.0, 132.2, 130.2, 129.3, 123.8, 123.2, 83.4, 57.9, 53.1, 52.8, 14.0.

MS (ESI): *m*/*z* = 278 [M + H^+].

Anal. Calcd for $C_{14}H_{15}NO_5$: C, 60.64; H, 5.45; N, 5.05. Found: C, 60.75; H, 5.49; N, 5.12.

Supporting Information

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

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