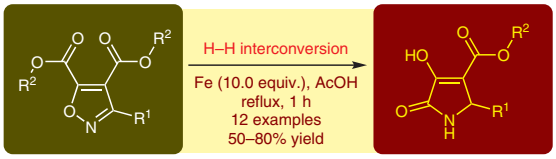
Synlett P. Kamath et al. Letter

Heterocycle–Heterocycle Strategy for 4,5-Disubstituted Pyrrolidine 2,3-Diones: Reductive Rearrangement Approach from Isoxazole Esters

Prashantha Kamath[a,b]
Vaibhav Jadhav[a]
Mukul Lal[*a,b]

[a] Syngenta Biosciences Pvt. Ltd. Santa Monica Works, Corlim, Ilhas, Goa 403110, India
mukul.lal@syngenta.com
[b] Department of Chemistry, Mangalore University, Mangalagangothri, 574199, Karnataka, India



Received: 10.04.2021
Accepted after revision: 27.04.2021
Published online: 27.04.2021
DOI: 10.1055/a-1492-8216; Art ID: st-2021-l0137-l
Crowd-Reviewed

Abstract The work demonstrates the heterocycle–heterocycle interconversion strategy to access 4,5-disubstituted 3-hydroxy-2-pyrrolidinone in moderate to good yields (50–80%). The approach has a distinct advantage over a multicomponent reaction approach as it allows access to unsubstituted 3-hydroxy-2-pyrrolidinone at the nitrogen position for further functionalization.

Key words isoxazoles, pyrrolidinones, reductive rearrangement, heterocycle–heterocycle strategy, (3+2) cycloaddition, MCR

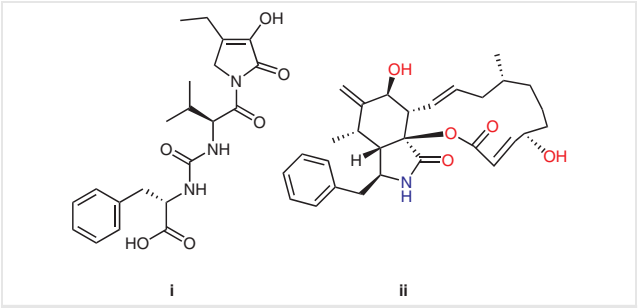
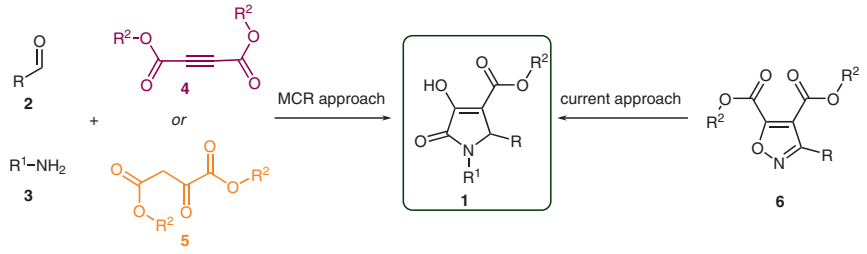


Figure 1 Naturally occurring leopoilic acid A (**i**) and cytochalasin B (**ii**)

Access to polysubstituted nitrogen heterocycles are crucial to the discovery of novel biologically active compounds (Figure 1).[1] Pyrrolidinones, including 3-hydroxy-2-pyrrolidinones, are one such class of nitrogen heterocycles being actively pursued for their biological activity ranging from HIV-1 inhibitors,[2] antitumor oral drugs,[3] antimicrobial,[4] and antibacterial applications.[5] Recently, they have been accessed via a multicomponent reaction (MCR) approach requiring an aldehyde, substituted aniline, and either acetylene dicarboxylates or 2-oxo-1,4-dicarboxylates. The MCR provides a convenient approach to 2-arylated 4-hydroxy-5-pyrrolidinones (Scheme 1).[6]

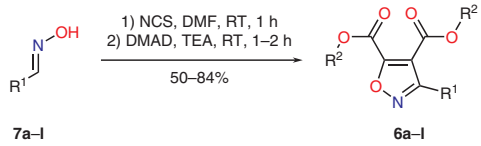
With our ongoing interest in heterocycle–heterocycle (H–H) interconversion strategy[7] we became interested to extend the H–H strategy to access 5-aryl/alkyl-substituted 3-hydroxy-2-pyrrolidinones via re-organization of the corresponding isoxazoles under reducing conditions (Scheme 1).

The isoxazoles needed for the study were prepared via the (3+2) cycloaddition of the corresponding nitrile oxides with dimethyl acetylene dicarboxylate (symmetrically substituted acetylene) at room temperature in moderate to good yields (50–84%, Scheme 2).[8]



Scheme 1 Literature-known multicomponent reaction approach to 2-pyrrolidinones and the current planned H–H approach to 2-pyrrolidinones

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany



Scheme 2 Synthesis of isoxazole derivatives **6a–l** via a (3+2) cycloaddition on dimethyl acetylenedicarboxyalte (DMAD)

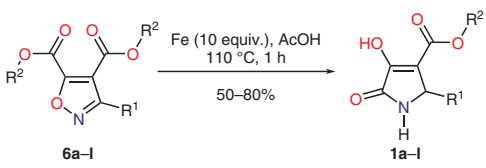
In general, the yield for isoxazole formation was relatively higher for electron-withdrawing substituents on the aryl rings than in the presence of electron-donating substituents on the ring. The low yield for the (3+2) cycloaddition in electron-donating nitrile oxide can be attributed to self-dimerization of nitrile oxides.[9]

Attempt to carry out reductive reorganization of isoxazoles **6a–l**[10] to 2-pyrrolidinones **1a–l** was initially optimized with **6a** as model substrate with iron as choice of reductant (Scheme 3).[11] Reductive rearrangement of **5a** to **1a** was not observed when the reaction was carried out with ammonium chloride as additive and ethanol as solvent, even after prolonged heating at 80 °C (5 equiv.; Table 1, entry 1).

Table 1 Optimization of the Reductive Rearrangement of **6** to **1**

Entry	Solvent	Reductant (equiv.)	Temp (°C)	Time (min)	Conversion (yield, %)
1	EtOH	Fe/NH_4Cl (5)	80	300	no reaction
2	EtOH	Zn/NH_4Cl (5)	80	300	no reaction
3	EtOH	Fe/HCl (5)	80	300	multiple spots
4	AcOH	Fe (5)	110	300	50
5	AcOH	Fe (10)	110	60	100 (71)
6	AcOH	Fe (10)	110	120	100 (65)
7	EtOH	Pd/C, H_2 (5 bar)	110	120	multiple spots

Replacement of either the reductant, i.e., iron with zinc, or the additive, i.e., ammonium chloride with hydrochloric acid, did not yield the desired product (entry 2, Table 1). With hydrochloric acid as additive the starting material was consumed albeit with extensive degradation of **6a** within 5 h at 80 °C (entry 3, Table 1).



Scheme 3 Reductive rearrangement of **6a–l** to **1a–l** in the presence of iron as reductant and acetic acid as solvent

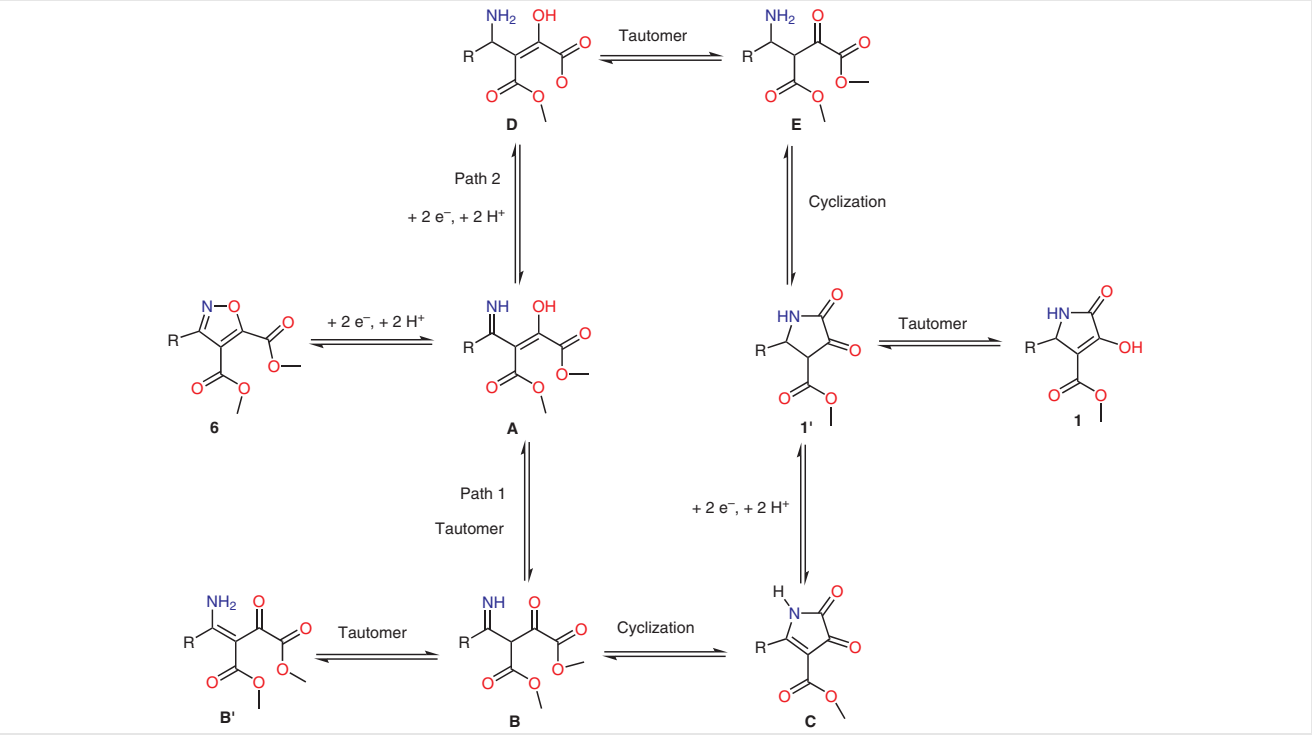
To our surprise, replacing ethanol with acetic acid as reaction solvent, formation of **1a** was observed (no additive) at reflux, however, with conversion of only 50% even after 5 h (entry 4, Table 1). To accelerate the reaction, further optimization was carried out by doubling the reductant quantity from 5 equiv. to 10 equiv., and to our delight it gave **1a** in 71% yield within 1 h of the reaction time (entry 5, Table 1). When the reaction time was extended to 2 h, a 5–10% drop in yield was observed suggesting decomposition of product under these conditions (entry 6, Table 1). Attempts to carry out reductive reorganization under hydrogenating conditions did not yield **1a** despite consumption of staring material (entry 7, Table 1).

The optimized conditions for reductive reorganization (entry 5, Table 1), i.e., iron as reductant (10.0 equiv.) in acetic acid under reflux conditions for 1 h, were used for general applicability of the method on other isoxazoles **6b–l**. Indeed, formation of **1b–l** was observed in all the cases in moderate to good yields (50–80%, Table 2). Interestingly, trends in the yield after isolation of **1a–l** were similar to those observed in the synthesis of isoxazoles **6a–l**, i.e., electron-withdrawing groups on aryl ring at 2-position in **6a–l** gave higher yields of rearranged product (**1d–f**,**h**, Table 2) than alkyl/electron-donating substituents on the aryl ring (**1b**,**g**,**i**,**l**, Table 2).

This could be due to stabilization of the developing charge during the reduction step. It was also observed that the yield of alkyl-substituted isoxazole gave reasonable to good yields of **1** (**1c**,**k**, Table 2) under the reaction conditions.[12]

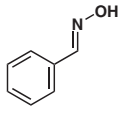
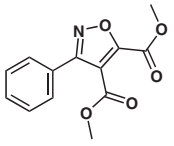
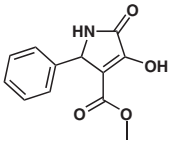
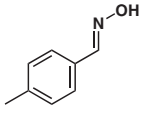
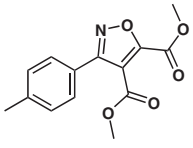
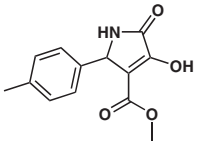
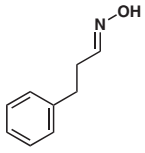
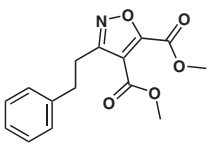
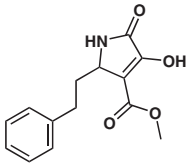
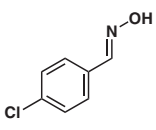
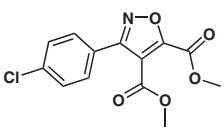
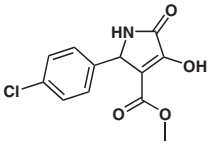
A plausible mechanism for the reductive rearrangement might be attributed to an initial SET between the reductant and **6** followed by protonation to form an intermediate **A**. Intermediate **A** could lead to the desired product following either path 1 or path 2 characterized by tautomerization, cyclization, and reduction. Path 1 involves an initial tautomerization (**B**), cyclization (**C**), reduction (**1′**), or path 2 involves further reduction (**D**), tautomerization (**E**), cyclisation (**1′**) and tautomerization to yield **1** (Scheme 4).

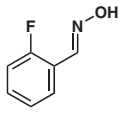
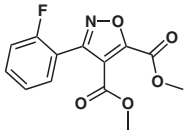
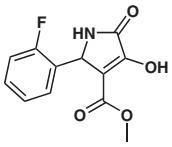
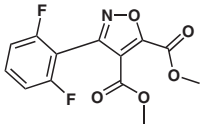
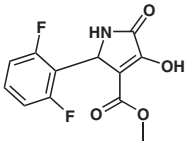
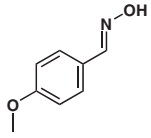
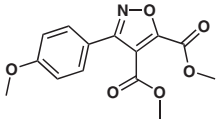
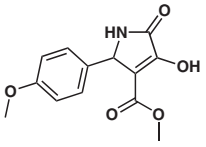
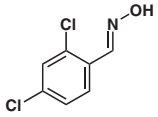
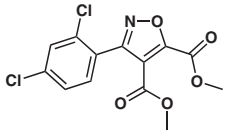
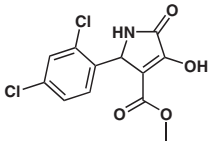
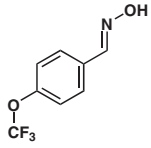
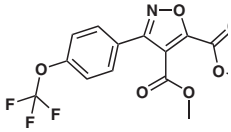
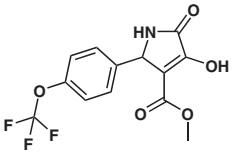
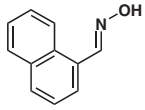
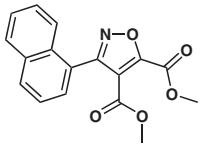
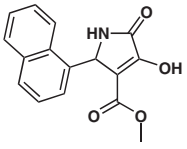
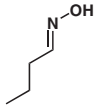
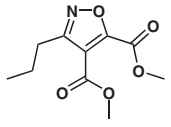
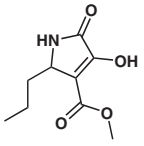
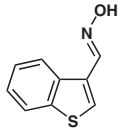
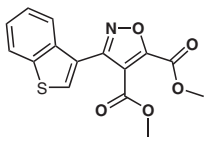
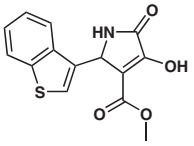
In conclusion the present work demonstrates the conversion of isoxazoles **6a–l**[10] into polysubstituted 2-pyrrolidinones (**1a–l**, 50–80% yield) under reductive rearrangement conditions with iron as reductant in acetic acid as solvent. The approach has a distinct advantage in accessing unsubstituted 2-pyrrolidinones at the nitrogen center allowing further scope of derivatization. The work further demonstrates the usefulness of heterocycle–heterocycle interconversion approach to access polysubstituted 2-pyrrolidinones from their corresponding isoxazoles. Further work is necessary to understand the overall mechanism and to exploit the full potential of this methodology.



Scheme 4 Plausible mechanism for the reductive rearrangement of isoxazoles **5** to 2-pyrrolidinone **1** using iron as reductant in acetic acid as solvent

Table 2 Synthesis of Isoxazole Esters **6a–l** by Cycloaddition of the Corresponding Oximes **7a–l** and Their Reductive Rearrangement to Pyrrolidine Diones **1a–l**

Entry	Oxime 7[a]	Isoxazole 6	Yield of 6 (%)	Pyrrolidine dione 1 (reduction)	Yield of 1 (%)
a			71		71
b			68		60
c			80		77
d			74		77

Entry	Oxime 7[a]	Isoxazole 6	Yield of 6 (%)	Pyrrolidine dione 1 (reduction)	Yield of 1 (%)
e			70		80
f			82		78
g			65		61
h			84		62
i			58		55
j			78		68
k			60		60
l			50		50

[a] Oximes **7a–l** were prepared using the literature protocol.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgment

The authors would like to thank Syngenta Biosciences Pvt. Ltd. for the support provided for carrying out the work under its PhD program.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-1492-8216.

References and Notes

(1) (a) Dhavan, A. A.; Kaduskar, R. D.; Musso, L.; Scaglioni, L.; Martino, P. A.; Dallavalle, S. *Beilstein J. Org. Chem.* **2016**, *12*, 1624. (b) Stork, G.; Nakahara, Y.; Nakahara, Y.; Greenlee, W. J. *J. Am. Chem. Soc.* **1978**, *24*, 7775. (c) Afsah, E. M.; Abdelmageed, S. M. *J. Heterocycl. Chem.* **2020**, *57*, 3763.

(2) (a) Ma, K.; Wang, P.; Fu, W.; Wan, X.; Zhou, L.; Chu, Y.; Ye, D. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 6724. (b) Pendri, A.; Troyer, T. L.; Sofia, M. J.; Walker, M. A.; Naidu, B. N.; Banville, J.; Meanwell, N. A.; Dicker, I.; Lin, Z.; Krystal, M.; Gerritz, S. W. *J. Comb. Chem.* **2010**, *12*, 84. (c) Zhuang, C.; Miao, Z.; Zhu, L.; Dong, G.; Guo, Z.; Wang, S.; Zhang, Y.; Wu, Y.; Yao, J.; Sheng, C.; Zhang, W. *J. Med. Chem.* **2012**, *55*, 9630.

(3) (a) Koz'minykh, V. O.; Igidov, N. M.; Zykova, S. S.; Kolla, V. E.; Shuklina, N. S.; Odegova, T. *Pharm. Chem. J. Khim. Farm. Zh.* **2002**, *36*, 188. (b) Anderson, D. R.; Stehle, N. W.; Kolodziej, S. A.; Reinhard, E. J. WO2004055015 (A1) **2014**. (c) Neo, A. G.; Marcos, C. F. *Org. Lett.* **2018**, *20*, 3875.

(4) Gein, V. L.; Armisheva, M. N.; Rassudikhina, N. A.; Voronina, E. V. *Pharm. Chem. J.* **2011**, *45*, 162.

(5) (a) Gein, V. L.; Mihalev, V. A.; Kasimova, N. N.; Voronina, E. V.; Vakhrin, M. I.; Babushkina, E. B. *Pharm. Chem. J.* **2007**, *41*, 208. (b) Levy, S. B.; Alekshun, M. N.; Podlogar, B. L.; Ohemeng, K.; Verma, A. K.; Warchol, T.; Bhatia, B.; Bowser, T.; Grier, M. US Patent Appl. US2005124678 (A1), 2005.

(6) (a) Saha, A.; Payra, S.; Banerjee, S. *RSC Adv.* **2016**, *6*, 101953. (b) Sarkar, R.; Mukhopadhyay, C. *Tetrahedron Lett.* **2013**, *54*, 3706. (c) Ghorbani-Vaghei, R.; Sarmast, N.; Mahmoodi, J. *Appl. Organomet. Chem.* **2017**, *31*, e3681. (d) Zonous, A. M.; Eskandari, I.; Notash, B. *Synth. Commun.* **2015**, *45*, 2115. (e) Castellano, T. G.; Neo, A. G.; Marcaccini, S.; Marcos, C. F. *Org. Lett.* **2012**, *14*, 6216. (f) Saha, M.; Das, A. R. *ChemistrySelect* **2017**, *2*, 10249. (g) Sun, J.; Wu, Q.; Xia, E.-Y.; Yan, C.-G. *Eur. J. Org. Chem.* **2011**, 2981. (h) Ahankar, H.; Ramazani, A.; Ślepokura, K.; Lis, T.; Woo Joo, S. *Green Chem.* **2016**, *18*, 3582. (i) Anary-Abbasinejad, M.; Mirhossaini, M.; Parhani, A.; Pourhassan, E. *Synth. Commun.* **2010**, *40*, 1350.

(7) Kamath, P.; Viner, R. C.; Smith, S. C.; Lal, M. *Synlett* **2017**, *28*, 1341.

(8) (a) Minakata, S.; Okumura, S.; Nagamachi, T.; Takeda, Y. *Org. Lett.* **2011**, *13*, 2966. (b) Mohammed, S.; Vishwakarma, R. A.; Harate, S. B. *RSC Adv.* **2015**, *5*, 3470.

(9) (a) Dubrovskiy, A. V.; Larcok, R. C. *Org. Lett.* **2010**, *12*, 1180. (b) Spiteri, C.; Sharma, P.; Zhang, F.; Macdonald, S. J. F.; Keeling, S.; Moses, J. E. *Chem. Commun.* **2010**, *46*, 1272.

(10) **General Procedure for the Synthesis of Isoxazoles 6**To a solution of oxime (1.0 mmol, 1.0 equiv.) in DMF (2.0 mL) at room temperature was added *N*-chlorosuccinimide (1.1 mmol, 1.1 equiv.) and stirred for 60 min. Dimethylacetylenedicarboxylate (DMAD) was added in one portion (1.1 mmol, 1.1 equiv.). Then, a solution of triethylamine (1.0 mmol, 1 equiv.) in DMF (1.0 mL) was added. The solution was stirred at RT till the reaction completes. The reaction mass poured into ice water, stirred for 10 min and extracted with ethyl acetate. The combined organic layer was washed with brine solution, dried over anhydrous sodium sulfate, and concentrated in vacuum. Purification if necessary was done by column chromatography using cyclohexane and ethyl acetate as mobile phase. §#BLD#§Dimethyl 3-Phenylisoxazole-4,5-dicarboxylate (6a)

(11) Prepared using the general procedure by starting with benzaldehyde oxime (3.0 mmol). Off-white solid, 71% yield; mp 62–64 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71–7.70 (d, *J* = 7.3 Hz, 2 H), 7.54–7.46 (m, 3 H), 4.10 (s, 3 H), 3.92 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.8, 161.2, 159.3, 156.4, 130.6, 128.8, 128.1, 126.8, 116.04, 53.3, 53.1 ppm. HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{13}H_{11}NO_5$: 261.0637; found: 261.0634.

(12) **General Procedure for the Synthesis of Pyrrolidine Diones 1a–l**

To a solution of isoxazole ester (0.5 g) in acetic acid (5.0 mL) was added portionwise Fe powder (10.0 equiv.) at 100 °C. During the addition, the colorless solution turned to dark brown. The reaction was monitored by LC–MS and after complete conversion the reaction mass was cooled to RT and poured into saturated aqueous sodium bicarbonate solution (50.0 mL). The mixture was filtered over a bed of Celite and the filtrate was extracted with diethyl ether before acidification with concd HCl to pH 1. During acidification the color of the solution turned from pale yellow to red and colorless at pH 1. The product was extracted to ethyl acetate layer and concentrated to get target molecule as solid (50–80%).

Methyl-4-hydroxy-5-oxo-2-phenyl-1,2-dihydropyrrole-3-carboxylate (1a)

Prepared using the general procedure by starting with dimethyl 3-phenylisoxazole-4,5-dicarboxylate (3.0 mmol). Off-white solid, 71% yield; decomposes above 140 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.44 (s, 1 H), 9.27 (s, 1 H), 7.35–7.18 (m, 5 H), 5.18 (s, 1 H), 3.53 (s, 3 H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6): δ = 166.3, 162.7, 154.2, 138.4, 128.3, 127.8, 127.1, 112.1, 56.4, 50.9 ppm. HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{12}H_{11}NO_4$: 233.0688; found: 233.0684.

(13) (a) Nagireddy, J. R.; Raheem, M.-A.; Haner, J.; Tam, W. *Curr. Org. Synth.* **2011**, *8*, 659. (b) Chen, Y.; Dong, H.; Zhang, H. *Chem. Eng. J.* **2018**, *352*, 501.