JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

Synthesis of α-Nitro Carbonyls via Nitrations in Flow

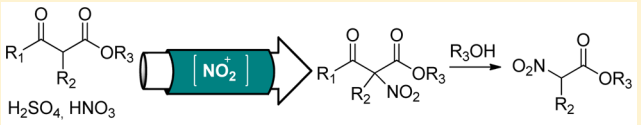
Anna Chentsova,[†,§] Dmitry B. Ushakov,[†,§] Peter H. Seeberger,[†,‡] and Kerry Gilmore*[,†]

[†]Department of Biomolecular Systems, Max-Planck-Institute of Colloids and Interfaces, Am Mühlenberg 1, 14476 Potsdam, Germany

[‡]Institute of Chemistry and Biochemistry, Freie Universität Berlin, Arnimallee 22, 14195 Berlin, Germany

Supporting Information

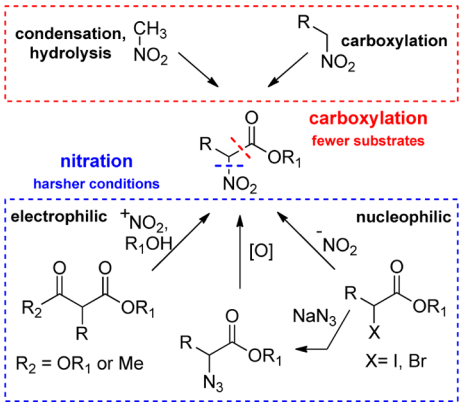
ABSTRACT: Reported is a safe, rapid method for the synthesis of α-nitro esters via the trapping of nitronium ions. The two-stage nitration and subsequent deacetylation of readily available 1,3-dicarbonyl compounds was achieved using a biphasic semicontinuous approach. α-Nitro esters and amides were obtained in good overall yields (53−84%). Some of the α-nitro-1,3-dicarbonyl intermediates exhibit enhanced reactivity and undergo an acid-catalyzed Nef-type reaction to α-oxo-carbonyls.



α-Nitro esters are valuable synthons in organic synthesis,[1] that can, due to their 1,3-dipole nature and the high acidity of the α-proton ($pK_a \sim 5.8$), be further transformed in a variety of ways.[2] They serve as carbon nucleophiles[3] and dipoles for heterocycle synthesis;[1a,4] they can form phenyliodonium or diazo ylide derivatives,[5] the latter of which can participate in NH insertion/Mannich-type reactions.[6] Moreover, α-nitro esters are intermediates for the synthesis of α-keto esters,[7] γ-oxo acids,[3f] as well α-amino acids.[5c,7,8]

Retrosynthetically, the α-nitro ester moiety offers two main disconnections (Scheme 1). The functionalization of a

Scheme 1. Synthetic Approaches for the Synthesis of α-Nitro Esters



nitroalkane with a CO_2 synthon,[9] is less common. One means of producing the unsubstituted α-nitro ester is the self-condensation of nitromethane under harsh basic conditions followed by an acid-catalyzed esterification.[10] Further alkylations or arylations of this core are possible.[8c,11]

More commonly, C−N bond formation is the key reaction. The nitro group can be introduced in either a nucleophilic or electrophilic manner. The most direct approach involves the treatment of α-haloesters with a nitrite anion.[12] However, the substrate scope of this route is limited[12a,13] and scavengers are required to avoid the formation of α-oximinoesters.[12b,14] Side product formation can be avoided through a two-step process, transforming α-haloesters via the corresponding α-azidoester (Scheme 1). The desired nitro derivatives are then generated under strong oxidizing conditions ($HOF{\cdot}CH_3CN$), rendering this approach less amenable to sensitive substrates, such as olefins and amines.[15]

The umpolung approach, where an electrophilic nitronium ion is captured by an enolizable nucleophile, expands the potential pool of starting materials to β-keto esters. Early work by Sifniades provided a homogeneous path, generating the key electrophile intermediate using an acetic anhydride/nitric acid mixture.[16] However, this approach is very temperature sensitive, resulting in side product formation and—disturbingly—the "ejection of the reaction mixture from the reaction vessel".[17]

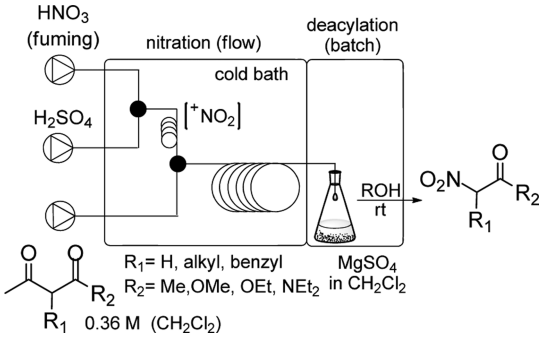
Biphasic systems where a mixture of sulfuric acid and nitric acid (or NH_4NO_3) was added to a chloroform solution of an acetoester at reduced temperatures offered better control over the reaction conditions.[17,18] The transformation requires vigorous stirring and careful temperature control over the 1 to 3 h it takes to complete. The resulting α-nitroacetate ester derivative is efficiently deacylated to give the nitro ester. While there are few published examples for this process,[16−19] continuous flow nitration of aromatic substrates has allowed for the safer handling of the corrosive strong acids,[20] improved temperature control inside the reactor,[21] and for the prevention of over-nitration.[22] In addition, biphasic reactions are significantly accelerated in flow due to the increased interfacial area between the phases. Precise control of the reaction conditions in meso-flow reactors should be a good basis for a general, safe, and broadly applicable process to generate valuable α-nitro esters.

The first step of the nitration/deacylation process (Scheme 2) is electrophile generation. The controlled formation of a

Received: July 7, 2016
Published: September 6, 2016

DOI: 10.1021/acs.joc.6b01634
J. Org. Chem. 2016, 81, 9415−9421

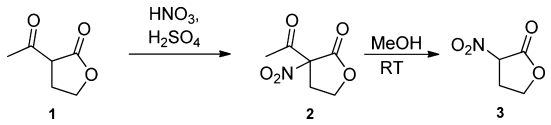
Scheme 2. Semi-Continuous Setup for the Nitration/Deacylation of 1,3-Dicarbonyl Compounds



nitronium ion occurred rapidly in a 30 μL PTFE (polytetrafluoroethylene) reactor at 10 °C upon mixing precooled fuming nitric acid (90+%, 1.2 equiv, 0.013 mL min^{-1}) and concentrated sulfuric acid (96%, 6 equiv, 0.080 mL min^{-1}). After a 19 s residence time, the stream of α-acetylbutyrolactone (**1**) in CH_2Cl_2 (0.36 M, 0.663 mL min^{-1}) was introduced via a T-mixer. The biphasic solution then passed through a second PTFE reactor (0.35 mL, 10 °C, residence time 28 s). The solution was quenched by addition of the exiting stream to a stirred suspension of $MgSO_4$ in CH_2Cl_2 at room temperature. After completion of the reaction, the quenching agent was filtered off and the solvent removed under reduced pressure. Deacylation occurred by addition and subsequent evaporation of methanol. ^1H NMR analysis revealed the desired α-nitrolactone **3** in 63% yield with 92% conversion (Table 1, entry 1).

Both an increase in the residence time using a larger second reactor (0.6 mL, entry 2) as well as the equivalents of nitric acid (entry 3) resulted in higher yields with complete conversion. While decreasing amounts of sulfuric acid did not improve the yield (70%, entry 4), an increase to 7.8 equiv (entry 5) afforded the desired compound in 79%. Further changes were not advantageous (entry 6). Use of more dilute nitric acid (65%) resulted in the drop in both conversion and yield (entry 7). After additional temperature screenings (entries 8−10), 1.4 equiv nitric acid and 7.8 equiv sulfuric acid at 10 °C were found to be optimal with an overall residence time of 54 s for the nitration (entry 11). The reaction was efficiently quenched with 1 g $MgSO_4$ per 1 mL acid solution.[23] The productivity of this process, following off-line deacylation, is 1.47 g/hour of the desired 3-nitrodihydrofuran-2(3H)-one (**3**).

Table 1. Optimization of Nitration/Deacylation of α-Acetylbutyrolactone (1)[a]



entry	HNO_3 equiv	H_2SO_4 equiv	res. time, (s)	T (°C)	conversion (%)[b]	yield (%)[b]
1	1.2	6	28[c]	10	92	63
2	1.2	6	48	10	> 95	70
3	1.4	6	47	10	> 95	74
4	1.4	4	49	10	> 95	70
5	1.4	7.8	46	10	> 95	79
6	1.4	10	44	10	> 95	74
7	1.4[d]	6.1	47	5	76	60
8	1.4	7.8	46	15	> 95	74
9	1.4	7.8	46	5	> 95	75
10	1.4	7.8	46	0	> 95	73
11	1.4	7.8	54[e]	10	> 95	80 (78%)[f]

[a]Reaction conditions: α-acetylbutyrolactone (**1**) in CH_2Cl_2 (0.36 M, 0.66 mL min^{-1}); reactor volume 0.6 mL, 96% H_2SO_4 and 90+% fuming HNO_3 were used unless indicated, equivalents with respect to α-acetylbutyrolactone (**1**); quench: 5 g $MgSO_4$ in 20 mL CH_2Cl_2, rt; deacylation via addition of 2 mL of methanol. [b]Determined using mesitylene as internal standard; yield over two steps. [c]Reactor volume 0.35 mL. [d]65% Nitric acid. [e]Reactor volume 0.7 mL. [f]Isolated yield in parentheses.

The optimized reaction conditions were tested on a range of 1,3-dicarbonyl compounds (Table 2). α-Substituted acetoacetates bearing an additional ester group gave the corresponding α-nitro esters in good yields (entries 1−2). Alkyl substituted substrates gave moderate [entries 3 (59%), 4 (53%)] to good yields (entry 5, 82%), with the *n*Bu chain requiring slightly higher amounts of acid to achieve full conversion (entry 6, 72%). Electron-withdrawing groups hinder the reaction, with ethyl 2-chloro-3-oxobutanoate (**16**) necessitating higher temperature (20 °C), a longer reaction time (107 s), and approximately twice as much acid (substrate: 0.2 M, entry 7).[24]

Several substrates suffer from competing reactions. Ethyl 2-benzylacetoacetate (**18**, entry 8) can also undergo electrophilic aromatic substitution, and the previously optimized conditions resulted in only 71% conversion with multiple substituted products. The reaction was pushed to completion by increasing the equivalents of acid (substrate: 0.16 M). The double nitrated scaffolds **19** (61%) and **20** (16%) were identified as the main products. This represents a limitation of the method, as nitration is believed to occur first at the aromatic ring due to the observation of the solely aryl-nitrated ethyl 2-(4-nitrobenzyl)-3-oxobutanoate (7%).

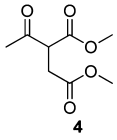
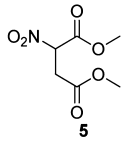
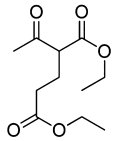
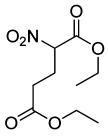
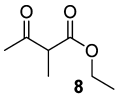
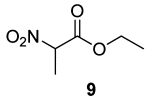
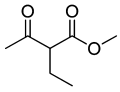
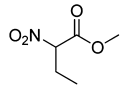
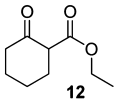
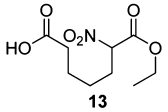
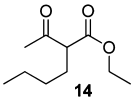
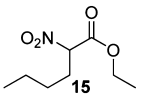
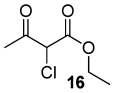
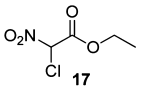
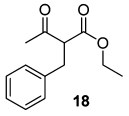
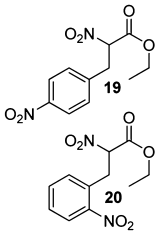
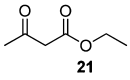
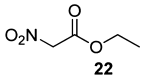
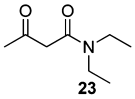
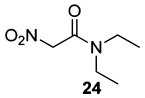
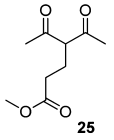
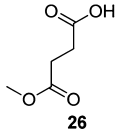
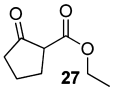
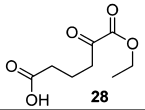
In the case of α-unsubstituted ethyl acetoacetate **21**, two competing pathways following nitration can occur due to the additional acidic proton: dimerization, which affords a substituted furoxan,[17] and dinitration of the α-position. These pathways could be partly suppressed using a more dilute nitronium ion solution (65% nitric acid) and a larger second reactor (1.8 mL), providing the desired ethyl 2-nitroacetate **22** in 70% yield (entry 9).[25]

Under the reaction conditions, several α-nitro acyl compounds exhibit enhanced reactivity resulting in the formation of different functional groups. Nitration of *N*,*N*-diethyl-3-oxobutanamide **23** gave a moderate yield of the α-nitro amide (entry 10, 54%) after a longer reaction time (107 s) and a change in the equivalents of nitronium ion (substrate: 0.2 M). One explanation for the lower yield is the formation, post-nitration, of two side products; one resulting from the *in situ* deacylation and dehydration of the nitro group (see Experimental Section for details).

No α-nitro product was observed for the 1,3-diacyl analog methyl 4-acetyl-5-oxohexanoate (**25**, entry 11). 4-Methoxy-4-oxobutanoic acid **26** was isolated as major product (34%). The formation of the carboxylic acid is not surprising as an *in situ* deacylation would result in the formation of a secondary α-nitro ketone, which is known to undergo fragmentation under strong acidic conditions to give the corresponding carboxylic acid.[26] The α-nitro ketone intermediate can also undergo a Nef reaction, as indicated by the isolation of small amounts both α-oxime- and α-oxo-ketone from the same reaction mixture.[27]

DOI: 10.1021/acs.joc.6b01634
J. Org. Chem. 2016, 81, 9415−9421

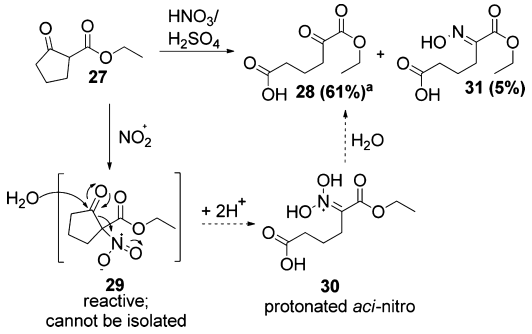
Table 2. Nitration/Deacylation of 1,3-Dicarbonyl Compounds in a Semi-Continuous Flow System[a]

Entry	Substrate	Product	Isolated yield (%)
1	 4	 5	75
2	 6	 7	75
3	 8	 9	59
4	 10	 11	53
5	 12	 13	82
6	 14	 15	72[b]
7	 16	 17	84[b,d,e]
8	 18	 19 20	61; 16[b,d]
9	 21	 22	70[c]
10	 23	 24	54[b,f]
11	 25	 26	34
12	 27	 28	61[d]

[a]Standard nitration conditions: 0.36 M solution in CH_2Cl_2 (0.663 mL min^{-1}); 10 °C; residence time 54 s; HNO_3 (90+%, 0.016 mL min^{-1}), H_2SO_4 (96%, 0.103 mL min^{-1}); for quenching and deacylation procedure see Experimental Section. Yield determined over two steps. [b]Higher amounts of acids used for complete conversion, see Experimental Section. [c]1 M solution in CH_2Cl_2 (0.4 mL min^{-1}), −5 to −3 °C; residence time 200 s; HNO_3 (65%, 0.031 mL min^{-1}), H_2SO_4 (96%, 0.110 mL min^{-1}). [d]Determined by NMR using mesitylene as internal standard. [e]Residence time 107 s, 20 °C. [f]Residence time 107 s.

Unexpectedly, this acid-catalyzed Nef reaction—which generally requires a nitronate intermediate—becomes the predominant pathway for ethyl 2-oxocyclopentanecarboxylate **27**. Compared to lactone **1**, where the α-nitro-γ-lactone is obtained in high yield, the cyclopentanone ester provides α-oxo-ester **28** in 61% yield (entry 12). This result can be explained assuming the formation of the protonated *aci*-nitro species **30** under strong acidic conditions, followed by a Nef reaction to give α-oxo-product **28** and oxime **31**—the latter of which was isolated in 5% yield (Scheme 3) and whose formation is known to be dependent on the pH of the reaction medium.[28]

Scheme 3. Proposed Pathway for the Formation of 6-Ethoxy-5,6-dioxohexanoic Acid (28) and Oxime (31)



[a]NMR yield using mesitylene as internal standard (47% isolated yield).

In conclusion, a rapid, facile, and safe procedure for the α-nitration of 1,3-dicarbonyls via a two-step nitration and deacylation process is disclosed. The controlled nitration in a continuous flow reactor occurs rapidly (54−200 s). Following the quenching of excess H_2SO_4/HNO_3 using $MgSO_4$, deacylation is achieved in methanol/ethanol in batch. A range of α-nitro esters/amides were produced with moderate-to-good yields (53−84%). Some α-nitro-1,3-dicarbonyl intermediates exhibit enhanced reactivity and under the reaction conditions yielding either Nef α-oxo products or carboxylic acids.

1. EXPERIMENTAL SECTION

General Information. All commercially available compounds and solvents were used without purification. Sulfuric acid (96%) and fuming nitric acid (90+%) were purchased from Roth (ROTIPURAN, 4623.4) and Acros (ACS reagent, A0332793), respectively. Acids and substrates were delivered into the reactor with the help of individual syringe pumps. Both flow reactors were built using polytetrafluoroethylene (PTFE) tubing (1.59 mm outer diameter, 0.76 mm inner diameter) and connected by ethylene tetrafluoroethylene (ETFE) T-mixers. All tubing, connectors, and adapters were purchased from IDEX Health and Science. All tubing and mixers were immersed in a water bath, cooled with the help of immersion cooler. Column chromatography was performed using Macherey-Nagel silica gel 60 M (0.04−0.063 mm). Preparative HPLC was performed using a semipreparative YMC-Pack Diol-300-NP column (150 × 20 mm).

DOI: 10.1021/acs.joc.6b01634
J. Org. Chem. 2016, 81, 9415−9421

The compounds were visualized by UV (254 nm) and by staining with an aqueous solution of potassium permanganate (prepared from 1.5 g $KMnO_4$ and 10 g K_2CO_3 in 1.25 mL 10% NaOH in 200 mL water). In describing ^1H and ^{13}C NMR spectra the following abbreviations were used to define the multiplicities (s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, t = triplet, dq = doublet of quartets, m = multiplet, br = broad), with coupling constants (J) in Hertz (Hz) and integration. Chemical shifts are reported in parts per million (ppm) relative to residual solvent peaks (δ) and are calibrated to the residual proton and carbon resonance of $CDCl_3$ (^1H: 7.24, ^{13}C: 77.16), CD_3OD (^1H: 3.31, ^{13}C: 49.00).[29] High-resolution mass spectra were obtained using ESI-Q-TOFmicro mass spectrometer and ESI-TOF mass spectrometer.

General Procedure for Nitration and Deacylation Step. Fuming nitric acid (90+%, 16 μL min^{-1}, 0.343 mmol/min) was mixed with sulfuric acid (96%, 103 μL min^{-1}, 1.85 mmol/min) at 10 °C (cooling bath was used) using a T-mixer. The resulting flow stream was passed through a 0.03 mL PTFE-tubing (0.76 mm inner diameter) and mixed with the solution of the α-acetyl compound (0.36 M in CH_2Cl_2, 0.663 mL min^{-1}, 0.239 mmol/min) using second T-mixer at the same temperature. The biphasic mixture was then passed through a 0.7 mL PTFE-tubing and collected in an Erlenmeyer flask containing a stirred suspension of $MgSO_4$ (5−10 g) in CH_2Cl_2 (20 mL) at room temperature. $MgSO_4$ was filtered off and the reaction mixture was concentrated under reduced pressure. If deacylation did not occur *in situ*, the following procedure was performed: the residue was dissolved in 30 mL of the corresponding alcohol (EtOH/MeOH) and stirred from 2 h to overnight (temperature varies from room temperature to reflux depending on the substrate). After completion of the reaction the solvent was removed under reduced pressure and the residue was purified by column chromatography.

*3-Nitrodihydrofuran-2(3H)-one (**3**).* General nitration procedure was used (0.6 mL (5.58 mmol) of α-acetylbutyrolactone (**1**) in CH_2Cl_2 (15 mL)). Quenching and deacylation procedure: for 11 mL of the collected solution, 5 g of $MgSO_4$ and 20 mL CH_2Cl_2 were used. The reaction mixture was filtered, treated with MeOH (2 mL), and concentrated under reduced pressure (30 °C). The residue was purified by column chromatography (*n*-hexane/ethyl acetate 25:1→9:1 *v*/*v*) to give compound **3** (405 mg, 78%) as an orange oil. R_f = 0.16 (*n*-hexane/ethyl acetate = 3:2 *v*/*v*); ^1H NMR (400 MHz, $CDCl_3$): 2.82 (dddd, J = 14.0, 9.0, 7.4, 4.8 Hz, 1H), 2.96 (dddd, J = 14.4, 8.5, 7.3, 7.3 Hz, 1H), 4.38 (ddd, J = 9.2, 7.3, 7.3 Hz, 1H), 4.56 (ddd, J = 8.8, 4.9, 4.9 Hz, 1H), 5.38 (dd, J = 9.0, 7.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 27.9, 66.9, 82.2, 167.2; HRMS (ESI): $[M + Na]^+$ calcd for $C_4H_5NO_4Na$: 154.0116, found 154.0106, $[M+K]^+$ calcd for $C_4H_5NO_4K$: 169.9856 found 169.9845.

*Dimethyl 2-Nitrosuccinate (**5**).* General nitration procedure was used (0.82 mL (5.05 mmol) of dimethyl 2-acetylsuccinate (**4**) in CH_2Cl_2 (13.2 mL)). Quenching and deacylation procedure: for 11 mL of the collected solution, 5 g of $MgSO_4$ and 20 mL CH_2Cl_2 were used, the reaction mixture was filtered and concentrated under reduced pressure. The residue was dissolved in 30 mL MeOH and stirred overnight at room temperature. The solvent was removed under reduced pressure and the residue was purified by column chromatography (*n*-hexane → *n*-hexane/ethyl acetate, 100:0→9:1 *v*/*v*) to give compound **5** (569 mg, 75%) as a yellow oil. R_f = 0.49 (*n*-hexane/ethyl acetate = 5:1 *v*/*v*); ^1H spectrum matches with the literature data.[30] ^1H NMR (400 MHz, $CDCl_3$): 3.16 (dd, J = 17.7, 4.9 Hz, 1H); 3.38 (dd, J = 17.7, 9.2 Hz, 1H), 3.75 (s, 3H), 3.87 (s, 3H), 5.57 (dd, J = 9.2, 4.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 34.4, 52.8, 54.1, 83.1, 164.2, 168.9. HRMS (ESI): $[M+Na]^+$ calcd for $C_6H_9NO_6Na$: 214.0328, found 214.0322.

*Diethyl 2-Nitropentanedioate (**7**).* General nitration procedure was used (1.0 mL (4.65 mmol) of diethyl 2-acetylpentanedioate (**6**) in CH_2Cl_2 (11.9 mL)). Quenching and deacylation procedure: for 10 mL of the collected solution, 5 g of $MgSO_4$ and 20 mL CH_2Cl_2 were used, the reaction mixture was filtered and concentrated under reduced pressure. The residue was dissolved in 30 mL EtOH and stirred overnight at room temperature. The solvent was removed under reduced pressure and the residue was purified by column chromatography (*n*-hexane/ethyl acetate 9:1→2:1 *v*/*v*) to give compound **7** (630 mg, 75%) as a colorless oil. R_f = 0.49 (*n*-hexane/ethyl acetate = 3:1 *v*/*v*); ^1H spectrum matches with the literature data.[31] ^1H NMR (400 MHz, $CDCl_3$): 1.26 (dd, J = 7.1, 7.1 Hz, 3H), 1.30 (dd, J = 7.1, 7.1 Hz, 3H), 2.39−2.61 (m, 4H), 4.15 (ddd, J = 7.1, 7.1, 7.1 Hz, 2H), 4.29 (ddd, J = 7.1, 7.1, 7.1 Hz, 2H), 5.27−5.32 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 14.0, 14.3, 25.4, 29.7, 61.1, 63.3, 86.8, 164.3, 171.6. HRMS (ESI): $[M+Na]^+$ calcd for $C_9H_{15}NO_6Na$: 256.0797, found 256.0809.

*Ethyl 2-Nitropropionate (**9**).* General nitration procedure was used (ethyl 2-methylacetoacetate (**8**) purity 95%, 0.75 mL (5.04 mmol) of substrate **8** in CH_2Cl_2 (13.25 mL)). Quenching and deacylation procedure: for 10 mL of the collected solution, 10 g of $MgSO_4$ and 20 mL CH_2Cl_2 were used, the reaction mixture was filtered and concentrated under reduced pressure. The residue was dissolved in 30 mL EtOH and stirred for 3 h at 80 °C (temperature of the oil bath). The solvent was removed under reduced pressure and the residue was purified by column chromatography (*n*-hexane/ethyl acetate 15:1→10:1 *v*/*v*) to give compound **9** (311 mg, 59%) as a yellow oil. R_f = 0.43 (*n*-hexane/ethyl acetate = 5:1 *v*/*v*). Obtained NMR matches with the literature data.[32] ^1H NMR (400 MHz, $CDCl_3$): 1.29 (t, J = 7.1 Hz, 3H), 1.77 (d, J = 7.2 Hz, 3H), 4.26 (q, J = 7.2 Hz, 2H), 5.19 (q, J = 7.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.0, 15.8, 63.1, 83.3, 165.2.

*Methyl 2-Nitrobutanoate (**11**).* General nitration procedure was used (0.72 mL (5.04 mmol) of methyl 2-ethylacetoacetate (**10**) in CH_2Cl_2 (13.28 mL)). Quenching and deacylation procedure: for 11 mL of the collected solution, 10 g of $MgSO_4$ and 20 mL CH_2Cl_2 were used, the reaction mixture was filtered and concentrated under reduced pressure. The residue was dissolved in 30 mL MeOH and stirred for 130 min at 65 °C (temperature of the oil bath). The solvent was removed under reduced pressure and the residue was purified by column chromatography (*n*-hexane/ethyl acetate 10:1→7:1 *v*/*v*) to give compound **11** (310 mg, 53%) as a yellow oil. R_f = 0.45 (*n*-hexane/ethyl acetate = 5:1 *v*/*v*); ^1H NMR (400 MHz, $CDCl_3$): 1.04 (dd, J= 7.4, 7.4 Hz, 3H), 2.14−2.36 (m, 2H), 3.83 (s, 3H), 5.05 (dd, J= 9.3, 5.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 10.3, 24.1, 53.6, 89.4, 165.1; HRMS (ESI): $[M+Na]^+$ calcd for $C_5H_9NO_4Na$: 170.0429, found 170.0419, $[M+K]^+$ calculated for $C_5H_9NO_4K$: 186.0169, found 186.0159. Compound **11** was previously synthesized.[9b]

*7-Ethoxy-6-nitro-7-oxoheptanoic Acid (**13**) and 7-Ethoxy-6-(hydroxyimino)-7-oxoheptanoic Acid (**13a**).* General nitration procedure was used (ethyl 2-oxocyclohexanecarboxylate (**12**) purity 95%, 0.85 mL (5.05 mmol) of substrate **12** in CH_2Cl_2 (13.15 mL)). Quenching and deacylation procedure: for 4 mL of the collected solution, 5 g of $MgSO_4$ and 20 mL CH_2Cl_2 were used, the reaction mixture was filtered and concentrated under reduced pressure. The residue was dissolved in 30 mL mixture of EtOH and water (2:1, *v*/*v*) and stirred overnight at 45 °C (temperature of the oil bath). The solvent was removed under reduced pressure and the residue was purified by column chromatography (DCM/MeOH 50:1→5:2 *v*/*v*) to give compound **13** (275 mg, 82%) as a yellow-green solid and compound **13a** (33.4 mg, 11%) as a yellow solid. Analytical data for compound **13**: R_f = 0.30 (DCM/MeOH = 30:1 *v*/*v*); mp 57−59 °C; ^1H NMR (400 MHz, $CDCl_3$):1.29 (t, J = 7.1 Hz, 3H), 1.40−1.49 (m, 2H) 1.66−1.74 (m, 2H), 2.10−2.19 (m, 1H), 2.24−2.32 (m, 1H), 2.36−2.39 (m, 2H), 4.27 (q, J = 7.1 Hz, 2H), 5.09 (dd, J = 9.3, 5.4 Hz, 1H), 9−12 (br signal COOH); ^{13}C NMR (100 MHz, $CDCl_3$) 13.9, 23.8, 25.0, 29.9, 33.5, 63.2, 87.9, 164.5, 179.5; HRMS (ESI): $[M+Na]^+$ calcd for $C_9H_{15}NO_6Na$ 256.0797, found 256.0796. Analytical data for compound **13a**: R_f = 0.5 (DCM/MeOH = 15:1 *v*/*v*); mp 98−100 °C; ^1H NMR (400 MHz, $CDCl_3$):1.33 (t, J = 7.1 Hz, 3H), 1.62−1.71 (m, 4H) 2.40 (t, J = 7.1 Hz, 2H), 2.66 (t, J = 7.2 Hz, 2H), 4.28 (q, J = 7.1 Hz, 2H), COOH and N−OH protons are not observed; ^{13}C NMR (100 MHz, $CDCl_3$) 14.1, 24.5, 24.6, 25.3,, 33.7, 62.0, 152.0, 163.2, 179.1; HRMS (ESI): $[M+Na]^+$ calcd for $C_9H_{15}NO_5Na$: 240.0848, found 240.0859.

*Ethyl 2-Nitrohexanoate (**15**).* Nitric acid (90+%, 16 μL/min, 0.343 mmol/min) was mixed with sulfuric acid (96%, 103 μL/min, 1.85 mmol/min) at 10 °C using a T-mixer. The resulting flow stream was

DOI: 10.1021/acs.joc.6b01634
J. Org. Chem. 2016, 81, 9415−9421

passed through a 0.03 mL PTFE-tubing and mixed with the ethyl 2-acetylhexanoate (**14**) solution (1.0 mL (5.11 mmol) of substrate **14** in CH_2Cl_2 (15 mL), 0.663 mL/min, 0.212 mmol/min) using second T-mixer at the same temperature. The biphasic mixture was passed through 0.7 mL PTFE-tubing and collected in an Erlenmeyer flask containing stirred suspension of $MgSO_4$ in CH_2Cl_2 (for 11 mL of the collected solution 5 g of $MgSO_4$ and 20 mL CH_2Cl_2 were used) at room temperature. The reaction mixture was filtered and concentrated under reduced pressure. The residue was dissolved in 30 mL EtOH and stirred overnight at room temperature. The solvent was removed under reduced pressure and the residue was purified by column chromatography (*n*-hexane → *n*-hexane/ethyl acetate, 100:0→9:1 *v*/*v*) to give compound **15** (480 mg, 72%) as a colorless oil. R_f = 0.49 (*n*-hexane/ethyl acetate = 2:1 *v*/*v*); ^{1}H NMR (400 MHz, $CDCl_3$): 0.90 (dd, *J* = 6.9, 6.9 Hz, 3H); 1.27 (dd, *J* = 7.1, 7.1 Hz, 3H), 1.32−1.42 (m, 4H), 2.05−2.15 (m, 1H), 2.18−2.31 (m, 1H), 4.25 (ddd, *J* = 7.1, 7.1, 7.1 Hz, 2H), 5.07 (dd, *J* = 9.4, 5.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 13.8, 14.0, 22.1, 27.8, 30.1, 63.1, 88.3, 164.8; HRMS (ESI): $[M+Na]^+$ calcd for $C_8H_{15}NO_4Na$: 212.0899, found 212.0887, $[M+K]^+$ calculated for $C_8H_{15}NO_4K$: 228.0638, found 228.0630. Compound **15** was previously synthesized.[15,33]

*Ethyl 2-Chloro-2-nitroacetate (**17**).* Nitric acid (90+%, 8 μL/min, 0.171 mmol/min) was mixed with sulfuric acid (96%, 52 μL/min, 0.923 mmol/min) at 20 °C using a T-mixer. The resulting acid mixture was passed through a 0.03 mL PTFE-tubing and mixed with the ethyl 2-chloro-3-oxobutanoate (**16**) solution (substrate **16** purity 95%, 0.23 mL (1.6 mmol) substrate **16** in CH_2Cl_2 (7.77 mL), 0.332 mL/min, 0.066 mmol/min) at the same temperature. The biphasic mixture was passed through 0.7 mL PTFE-tubing and collected in an Erlenmeyer flask containing stirred suspension of $MgSO_4$ in CH_2Cl_2 (for 4 mL of the collected solution 5 g of $MgSO_4$ and 20 mL CH_2Cl_2 were used) at room temperature. The reaction mixture was filtered and concentrated under reduced pressure. The residue was dissolved in 10 mL EtOH and stirred overnight at room temperature. The solvent was gently removed under reduced pressure (room temperature) to give volatile compound **17** as a yellow oil (84%, determined by ^{1}H NMR using mesitylene as internal standard). An analytically pure sample was obtained by column chromatography (*n*-hexane/ethyl acetate 20:1→10:1 *v*/*v*). R_f = 0.60 (*n*-hexane/ethyl acetate = 2:1 *v*/*v*); Obtained ^{1}H NMR matches with the literature data.[34] ^{1}H NMR (400 MHz, $CDCl_3$): 1.36 (t, *J* = 7.2 Hz, 3H), 4.39 (q, *J* = 6.7 Hz, 2H), 6.23 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 13.9, 64.9, 85.6, 160.7.

*Ethyl 2-Nitro-3-(4-nitrophenyl)propanoate (**19**), Ethyl 2-Nitro-3-(2-nitrophenyl)propanoate (**20**), and Ethyl 2-(4-Nitrobenzyl)-3-oxobutanoate (**20a**).* Nitric acid (90+%, 16 μL/min, 0.343 mmol/min) was mixed with sulfuric acid (96%, 103 μL/min, 1.852 mmol/min) at 10 °C using a T-mixer. The resulting acid mixture was passed through a 0.03 mL PTFE-tubing and mixed with the ethyl 2-benzylacetoacetate (**18**) solution (0.48 mL (2.26 mmol) of substrate **18** in CH_2Cl_2 (13.5 mL), 0.663 mL/min, 0.106 mmol/min) at the same temperature. The biphasic mixture was passed through 0.7 mL PTFE-tubing and collected in an Erlenmeyer flask containing stirred suspension of $MgSO_4$ in CH_2Cl_2 (for 11 mL of the collected solution, 5 g of $MgSO_4$ and 20 mL CH_2Cl_2 were used) at room temperature. The reaction mixture was filtered and concentrated under reduced pressure. The residue was dissolved in 30 mL EtOH and stirred overnight at 45 °C. The solvent was removed under reduced pressure to give compound **19** (61%), compound **20** (16%), and compound **20a** (7%). (Due to the tedious purification procedure, the yields were determined by ^{1}H NMR using mesitylene as an internal standard). Analytically pure samples of compound **20** as a yellow oil were obtained using purification by column chromatography (*n*-hexane/DCM 2:1→1:5 *v*/*v*). Compound **20a** was isolated as a yellow oil from the same column, however was unable to be separated from the impurities according to ^{1}H NMR. An analytically pure sample of compound **19** was obtained by purification using HPLC Hex/*i*PrOH (99:1, *v*/*v*). Analytical data for compound **19**: R_f = 0.33 (*n*-hexane/DCM 1:4 *v*/*v*); ^{1}H NMR (400 MHz, $CDCl_3$):1.30 (t, *J* = 7.1 Hz, 3H), 3.59 (dd, *J* = 14.8, 5.3 Hz, 1H), 3.68 (dd, *J* = 14.8, 9.5 Hz, 1H), 4.31 (q, *J* = 6.3 Hz, 2H), 5.36 (dd, *J* = 9.4, 5.7 Hz, 1H), 7.42 (d, *J* = 8.3 Hz, 2H), 8.20 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 14.0, 35.9, 63.8, 88.4, 124.4, 130.1, 141.6, 147.8 163.5; HRMS (ESI): $[M+Na]^+$ calcd for $C_{11}H_{12}N_2O_6Na$: 291.0593, found 291.0585. Analytical data for compound **20**: R_f = 0.63 (*n*-hexane/DCM 1:4 *v*/*v*); ^{1}H NMR (400 MHz, $CDCl_3$): 1.29 (t, *J* = 6.9 Hz, 3H), 3.71 (dd, *J* = 14.3, 9.8 Hz, 1H), 3.90 (dd, *J* = 14.4, 4.9 Hz, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 5.66 (dd, *J* = 9.7, 5.0 Hz, 1H), 7.36 (d, *J* = 7.6 Hz, 1H), 7.50 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.59 (dd, *J* = 7.5, 7.5 Hz, 1H), 8.11 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 14.0, 34.4, 63.5, 88.1, 125.9, 129.6, 129.7, 133.5, 134.2, 148.9, 163.8; HRMS-ESI: $[M+Na]^+$ calcd for $C_{11}H_{12}N_2O_6Na$ 291.0593 found 291.0591. Analytical data for compound **20a**: Obtained NMR matches with the literature data.[35] R_f = 0.20 (*n*-hexane/DCM 1:4 *v*/*v*); ^{1}H NMR (400 MHz, $CDCl_3$): 1.22 (t, *J* = 7.2 Hz, 3H), 2.24 (s, 3H), 3.25 (t, *J* = 7.6 Hz, 2H), 3.78 (t, *J* = 8.0, 1H), 4.12−4.21 (m, 2H), 7.36 (d, *J* = 8.8 Hz, 2H), 8.14 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 14.2, 29.7, 33.6, 60.8, 62.0, 123.9, 129.9, 146.2, 147.0, 168.6, 201.3.

*Ethyl 2-Nitroacetate (**22**).* Nitric acid (65%, 31 μL/min, 0.657 mmol/min) was mixed with sulfuric acid (96%, 110 μL/min, 1.972 mmol/min) at −5→−3 °C using a T-mixer ($EtOH/N_2$ bath was used, volume of the loop before second T-mixer 0.5 mL). The resulting acid mixture was passed through a 0.03 mL PTFE-tubing and mixed with the ethyl acetoacetate (**21**) solution (6.5 mL (49 mmol) of substrate **21** in CH_2Cl_2 (42.5 mL), 0.4 mL/min, 0.4 mmol/min) at the same temperature. The biphasic mixture was passed through 1.8 mL PTFE-tubing and collected in an Erlenmeyer flask containing stirred suspension of $MgSO_4$ in CH_2Cl_2 (40.5 mL of solution was collected, 21 g of $MgSO_4$ was used: for 1 mL of the pumped H_2SO_4 2 g of $MgSO_4$ was used) at room temperature, the reaction mixture was filtered, dried over Na_2SO_4, treated with EtOH (1:1 *v*/*v*) and concentrated under reduced pressure (30 °C). The residue was purified using Kugelrohr distillation at 100 °C, 11 mbar to give compound **22** (3.8 g, 70%) as a yellow oil. In addition, 22% (determined by NMR using mesitylene as an internal standard) of 3,4-bis(ethoxycarbonyl)-1,2,5-oxadiazole 2-oxide (**22b**)[4c] was observed. Analytical data for compound **22**: ^{1}H NMR (400 MHz, $CDCl_3$): 1.28 (t, *J* = 7.2 Hz, 3H), 4.27 (q, *J* = 7.1 Hz, 2H), 5.14 (s, 2H); ^{13}C spectrum matches with the literature data.[36] ^{13}C NMR (100 MHz, $CDCl_3$): 13.9, 63.3, 76.4, 162.1; HRMS (ESI): $[M+Na]^+$ calcd for $C_4H_7NO_4Na$: 156.0273, found 156.0252.

*N,N-Diethyl-2-nitroacetamide (**24**), N,N-Diethyl-2-(hydroxyimino)-3-oxobutanamide (**24a**), 3,4-Bis(diethylcarbamoyl)-1,2,5-oxadiazole 2-Oxide (**24b**).* Nitric acid (90+%, 8 μL/min, 0.171 mmol/min) was mixed with sulfuric acid (96%, 52 μL/min, 0.923 mmol/min) at 10 °C using a T-mixer. The resulting acid mixture was passed through a 0.03 mL PTFE-tubing and mixed with *N,N*-diethyl-3-oxobutanamide (**23**) solution (0.16 mL (1.01 mmol) of substrate **23** in CH_2Cl_2 (4.84 mL), 0.332 mL/min, 0.066 mmol/min) at the same temperature. The biphasic mixture was passed through 0.7 mL PTFE-tubing and collected in an Erlenmeyer flask containing stirred suspension of $MgSO_4$ in CH_2Cl_2 (for 4 mL of the collected solution, 5 g of $MgSO_4$ and 20 mL CH_2Cl_2 were used) at room temperature. The reaction mixture was filtered and concentrated under reduced pressure. Crude reaction mixture was purified by column chromatography (*n*-hexane/ethyl acetate 5:1→1:1 *v*/*v*) to give compound **24** (68.7 mg, 54%) as a yellow oil, compound **24b** (23.4 mg, 10%) as a yellow oil and compound **24a** (16.7 mg, 11%) as a light peach clear solid. Analytical data for compound **24**: R_f = 0.19 (*n*-hexane/ethyl acetate = 2:1 *v*/*v*); ^{1}H NMR (400 MHz, $CDCl_3$): 1.17 (t, *J* = 7.1 Hz, 3H), 1.23 (t, *J* = 7.1 Hz, 3H), 3.24 (q, *J* = 7.2 Hz, 2H), 3.44 (q, *J* = 7.1 Hz, 2H), 5.27 (s, 2H); ^{13}C NMR (100 MHz, CD_3OD): 12.9, 14.2, 42.0, 43.3, 78.3, 163.2; HRMS (ESI): $[M+Na]^+$ calcd for $C_6H_{12}N_2O_3Na$: 183.0746, found 183.0740. Analytical data for compound **24a**: R_f = 0.07 (*n*-hexane/ethyl acetate = 2:1 *v*/*v*); Obtained NMR matches with literature data.[37] ^{1}H NMR (400 MHz, $CDCl_3$): 1.12 (t, *J* = 7.0 Hz, 3H), 1.22 (t, *J* = 7.6 Hz, 3H), 2.39 (s, 3H), 3.12 (q, *J* = 6.7 Hz, 2H), 3.52 (q, *J* = 7.0 Hz, 2H), 11.64 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 12.7, 14.0, 25.7, 39.3, 42.9, 152.4, 164.2, 195.2. Analytical data for compound **24b:** R_f = 0.31 (*n*-hexane/ethyl acetate =2:1 *v*/*v*); ^{1}H NMR (400 MHz, $CDCl_3$): 1.18−1.32 (m,

DOI: 10.1021/acs.joc.6b01634
J. Org. Chem. 2016, 81, 9415−9421

12H), 3.31 (q, J = 7.2 Hz, 2H), 3.48−3.55 (m, 4H), 3.59 (q, J = 7.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 12.6, 12.7, 14.4, 14.7, 40.5, 41.1, 43.3., 43.8, 111.5, 152.3, 154.8, 156.8; HRMS (ESI): $[M+Na]^+$ calcd for $C_{12}H_{20}N_4O_4Na$: 307.1382, found 307.1372, $[M+K]^+$ calcd for $C_{12}H_{20}N_4O_4K$: 323.1122, found 323.1111.

*4-Methoxy-4-oxobutanoic Acid (**26**), Methyl 4,5-Dioxohexanoate (**26a**), Methyl 4-(Hydroxyimino)-5-oxohexanoate (**26b**).* General nitration procedure was used (0.38 mL (2.16 mmol) of substrate **25** in CH_2Cl_2 (5.62 mL)). Quenching and deacylation procedure: for 4 mL of the collected solution, 5 g of $MgSO_4$ and 20 mL CH_2Cl_2 were used, the reaction mixture was filtered and concentrated under reduced pressure. Crude was purified by column chromatography (*n*-hexane/ethyl acetate 5:1→1:1 and then DCM → DCM/MeOH 100:1→60:1→5:1 *v*/*v*) to give compound **26** (65.4 mg, 34%) as an yellow oil together with compound **26a** (5.6 mg, 3%) as a yellow oil, and compound **26b** (22.0 mg, 9%) as a white amorphous solid. Additionally unreacted starting material was identified by ^{1}H NMR but was not isolated due to tedious purification procedure. Analytical data for compound **26**: Obtained NMR matches with the literature data.[38] ^{1}H NMR (400 MHz, $CDCl_3$): 2.60−2.69 (m, 4H), 3.69 (s, 3H), 8.5−9.5 (br, COOH); ^{13}C NMR (100 MHz, $CDCl_3$): 28.8, 29.1, 52.1, 172.8, 178.4. Analytical data for compound **26a**: R_f = 0.4 (*n*-hexane/ethyl acetate =4:1 *v*/*v*); ^{1}H NMR (600 MHz, $CDCl_3$): 2.36 (s, 3H), 2.66 (t, J = 6 Hz 2H), 3.03 (t, J = 6 Hz, 2H), 3.69 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): 23.8, 27.8, 30.9, 52.1, 172.9, 197.1, 197.6; HRMS (ESI): $[M+Na]^+$ calcd for $C_7H_{10}O_4Na$: 181.0477, found 181.0478. Compound **26a** was previously synthesized.[39] Analytical data for compound **26b**: R_f = 0.37 (DCM/MeOH = 30:1 *v*/*v*); ^{1}H NMR (400 MHz, $CDCl_3$): 2.37 (s, 3H), 2.52 (t, J = 7.8 Hz, 2H), 2.84 (t, J = 7.7 Hz, 2H), 3.67 (s, 3H), 7.89 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 18.2, 25.4, 30.2, 52.0, 158.8, 173.2, 196.7; HRMS (ESI): $[M+Na]^+$ calcd for $C_7H_{11}NO_4Na$: 196.0586, found 196.0579, $[M+K]^+$ calcd for $C_7H_{11}NO_4K$ 212.0325, found 212.0322.

*6-Ethoxy-5,6-dioxohexanoic Acid (**28**), 6-Ethoxy-5-(hydroxyimino)-6-oxohexanoic Acid (**31**), 6-Ethoxy-5-nitro-6-oxohexanoic Acid (**28b**).* General nitration procedure was used (0.75 mL (5.06 mmol) of ethyl 2-oxocyclopentanecarboxylate (**27**) in CH_2Cl_2 (13.25 mL)). Quenching and deacylation procedure: for 11 mL of the collected solution, 10 g of $MgSO_4$ and 20 mL CH_2Cl_2 were used, the reaction mixture was filtered and concentrated under reduced pressure. Analysis of crude ^{1}H NMR revealed formation of 6-ethoxy-5,6-dioxohexanoic acid (**28**) with the 61% yield determined by ^{1}H NMR using mesitylene as internal standard. Presumably ethyl 1-nitro-2-oxocyclopentanecarboxylate (**29**) was formed, as suggested by the ^{1}H NMR spectrum (^{1}H NMR (400 MHz, $CDCl_3$): 2.05−2.13 (m, 2H), 2.53−2.61 (m, 2H), 2.81 (dt, J = 14.5, 7.3 Hz, 1H), 2.96 (dt, J = 14.0, 6.8 Hz, 1H), peaks corresponding to EtO-group are overlapping with EtO-group of another compound) which, upon standing, spontaneously undergoes a ring-opening reaction with atmospheric water to give compound **28b**. The residue was purified by column chromatography (*n*-hexane/ethyl acetate 15:1→10:1 and then DCM/MeOH 60:1→15:1 *v*/*v*) to give compound **28** (353 mg, 47%) as a yellow oil, oxime **31** (42.2 mg, 5%) as a white solid and compound **28b** (33 mg, 4%) as a white solid. Analytical data for compound **28**: R_f = 0.45 (DCM/MeOH = 15:1 *v*/*v*/*v*); Analytical data for the compound **28** matches with the literature data.[40] ^{1}H NMR (400 MHz, $CDCl_3$): 1.37 (t, J = 7.1 Hz, 3H), 1.97 (quin, J = 7.2 Hz, 2H), 2.44 (t, J = 7.2 Hz, 2H), 2.95 (t, J = 7.1 Hz, 2H), 4.32 (q, J = 7.1 Hz, 2H), 9−11 (br signal COOH); ^{13}C NMR (100 MHz, $CDCl_3$): 14.0, 17.9, 32.6, 38.2, 62.6, 160.8, 179.2, 193.7. Analytical data for compound **31**: R_f = 0.31 (DCM/MeOH = 15:1 *v*/*v*/*v*); mp 106−108 °C; ^{1}H NMR: (400 MHz, $CDCl_3$): 1.35 (t, J = 7.1 Hz, 3H), 1.96 (p, J = 6.9 Hz, 2H), 2.45 (t, J = 6.9 Hz, 2H), 2.73 (t, J = 7.0 Hz, 2H), 4.30 (q, J = 7.1 Hz, 2H), 10−12 (br signal COOH), signal for N−OH proton is not observed; ^{13}C NMR (100 MHz, $CDCl_3$) 14.1, 21.0, 24.3, 33.6, 62.1, 151.9, 163.2, 178.2; HRMS (ESI): $[M+Na]^+$ calcd for $C_8H_{13}NO_5Na$ 226.0691, found 226.0686. Analytical data for compound **28b**: R_f = 0.48 (DCM/MeOH = 15:1 *v*/*v*/*v*); mp 47−49 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 1.31 (dd, J = 7.1, 7.1 Hz, 3H), 1.67−1.80 (m, 2H), 2.18−2.27 (m, 1H), 2.29−2.39 (m, 1H), 2.46 (t, J = 7.1 Hz, 2H), 4.29 (ddd, J = 7.1, 7.1, 7.1 Hz, 2H), 5.12 (dd, J = 9.3, 5.5 Hz, 1H), 10−12 (br signal COOH); ^{13}C NMR (100 MHz, $CDCl_3$) 14.0, 20.8, 29.5, 33.0, 63.3, 87.8, 164.4, 178.7; HRMS (ESI): $[M-H]^+$ calcd for $C_8H_{12}NO_6$: 218.0665, found 218.0686.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01634.

^{1}H and ^{13}C NMR spectra for all new compounds and optimization experiments to determine minimum amount of desiccant needed for the quenching procedure (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: kerry.gilmore@mpikg.mpg.de

Author Contributions

§A.C. and D.B.U. contributed equally to this work

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge the financial support of the Max Planck Society. We also thank Fabian Klautzsch and Sebastian Schmid for recording high-resolution mass spectra.

■ REFERENCES

(1) (a) Kislyi, V. V.; Samet, A. V.; Semenov, V. V. *Curr. Org. Chem.* **2001**, *5*, 553−570. (b) Tietze, L. F.; Schneider, C. In *Encyclopedia of Reagents for Organic Synthesis*; John Wiley & Sons, Ltd, 2001. (c) Shipchandler, M. *Synthesis* **1979**, *1979*, 666−686.

(2) Goumont, R.; Magnier, E.; Kizilian, E.; Terrier, F. *J. Org. Chem.* **2003**, *68*, 6566−6570.

(3) (a) Ji, C.-B.; Liu, Y.-L.; Cao, Z.-Y.; Zhang, Y.-Y.; Zhou, J. *Tetrahedron Lett.* **2011**, *52*, 6118−6121. (b) Luzzio, F. A. *Tetrahedron* **2001**, *57*, 915−945. (c) Parise, L.; Pelagalli, A.; Pellacani, L.; Sciubba, F.; Vergari, M. C.; Fioravanti, S. *J. Org. Chem.* **2016**, *81*, 2864−2874. (d) Zhang, S.; Xu, K.; Guo, F.; Hu, Y.; Zha, Z.; Wang, Z. *Chem. - Eur. J.* **2014**, *20*, 979−982. (e) Zhou, Y.; Liu, Q.; Gong, Y. *Tetrahedron Lett.* **2013**, *54*, 3011−3014. (f) Aginagalde, M.; Bello, T.; Masdeu, C.; Vara, Y.; Arrieta, A.; Cossio, F. P. *J. Org. Chem.* **2010**, *75*, 7435−7438. (g) Lin, S.; Li, M.; Dong, Z.; Liang, F.; Zhang, J. *Org. Biomol. Chem.* **2014**, *12*, 1341−1350. (h) Dauzonne, D.; Royer, R. *Synthesis* **1983**, *1983*, 836−837. (i) Xu, J.; Ai, J.; Liu, S.; Peng, X.; Yu, L.; Geng, M.; Nan, F. *Org. Biomol. Chem.* **2014**, *12*, 3721−3734.

(4) (a) Gangadhara Chary, R.; Rajeshwar Reddy, G.; Ganesh, Y. S. S.; Vara Prasad, K.; Raghunadh, A.; Krishna, T.; Mukherjee, S.; Pal, M. *Adv. Synth. Catal.* **2014**, *356*, 160−164. (b) Chen, K.-P.; Chen, Y.-J.; Chuang, C.-P. *Eur. J. Org. Chem.* **2010**, *2010*, 5292−5300. (c) Trogu, E.; Cecchi, L.; De Sarlo, F.; Guideri, L.; Ponticelli, F.; Machetti, F. *Eur. J. Org. Chem.* **2009**, *2009*, 5971−5978. (d) Guideri, L.; De Sarlo, F.; Machetti, F. *Chem. - Eur. J.* **2013**, *19*, 665−677. (e) Baranov, M. S.; Yampolsky, I. V. *Tetrahedron Lett.* **2013**, *54*, 628−629. (f) Nakamura, S.; Sugimoto, H.; Ohwada, T. *J. Am. Chem. Soc.* **2007**, *129*, 1724−1732.

(5) (a) Xu, X.; Lu, H.; Ruppel, J. V.; Cui, X.; Lopez de Mesa, S.; Wojtas, L.; Zhang, X. P. *J. Am. Chem. Soc.* **2011**, *133*, 15292−15295. (b) Moreau, B.; Alberico, D.; Lindsay, V. N. G.; Charette, A. B. *Tetrahedron* **2012**, *68*, 3487−3496. (c) Moreau, B.; Charette, A. B. *J. Am. Chem. Soc.* **2005**, *127*, 18014−18015. (d) Charette, A. B.; Wurz, R. P.; Ollevier, T. *Helv. Chim. Acta* **2002**, *85*, 4468−4484. (e) Charette, A. B.; Wurz, R. *J. Mol. Catal. A: Chem.* **2003**, *196*, 83−91.

DOI: 10.1021/acs.joc.6b01634
J. Org. Chem. 2016, 81, 9415−9421

(6) (a) So, S. S.; Mattson, A. E. *J. Am. Chem. Soc.* **2012**, *134*, 8798−8801. (b) Yang, T.; Zhuang, H.; Lin, X.; Xiang, J.-N.; Elliott, J. D.; Liu, L.; Ren, F. *Tetrahedron Lett.* **2013**, *54*, 4159−4163.
(7) Metz, A. E.; Kozlowski, M. C. *J. Org. Chem.* **2013**, *78*, 717−722.
(8) (a) Young, A. J.; White, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 14090−14091. (b) Chen, Z.; Morimoto, H.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 2170−2171. (c) Singh, A.; Yoder, R. A.; Shen, B.; Johnston, J. N. *J. Am. Chem. Soc.* **2007**, *129*, 3466−3467. (d) He, L.; Srikanth, G. S. C.; Castle, S. L. *J. Org. Chem.* **2005**, *70*, 8140−8147. (e) Singh, A.; Johnston, J. N. *J. Am. Chem. Soc.* **2008**, *130*, 5866−5867. (f) Ram, S.; Ehrenkaufer, R. E. *Synthesis* **1986**, *1986*, 133−135.
(9) (a) Reddy, G. R.; Mukherjee, D.; Chittoory, A. K.; Rajaram, S. *Org. Lett.* **2014**, *16*, 5874−5877. (b) Lehr, F.; Gonnermann, J.; Seebach, D. *Helv. Chim. Acta* **1979**, *62*, 2258−2275.
(10) (a) Zen, S.; Koyama, M.; Koto, S. In *Org. Synth.*; John Wiley & Sons, Inc., 2003. (b) Matthews, V.; Kubler, D. *J. Org. Chem.* **1960**, *25*, 266−268.
(11) (a) Lyttle, D. A.; Weisblat, D. I. *J. Am. Chem. Soc.* **1947**, *69*, 2118−2119. (b) Snyder, B. H. R.; Katz, L. *J. Am. Chem. Soc.* **1947**, *69*, 3140−3142. (c) Genet, J. P.; Ferround, D. *Tetrahedron Lett.* **1984**, *25*, 3579−3582. (d) Fiandanese, V.; Naso, F.; Scilimati, A. *Tetrahedron Lett.* **1984**, *25*, 1187−1190. (e) Metz, A. E.; Berritt, S.; Dreher, S. D.; Kozlowski, M. C. *Org. Lett.* **2012**, *14*, 760−763.
(12) (a) Kornblum, N.; Chalmers, M. E.; Daniels, R. *J. Am. Chem. Soc.* **1955**, *77*, 6654−6655. (b) Kornblum, N.; Blackwood, R. K.; Powers, J. W. *J. Am. Chem. Soc.* **1957**, *79*, 2507−2509.
(13) Kornblum, N.; Weaver, W. M. *J. Am. Chem. Soc.* **1958**, *80*, 4333−4337.
(14) Simchen, G. *Liebigs Ann. Chem.* **1979**, *1979*, 628−638.
(15) Carmeli, M.; Rozen, S. *J. Org. Chem.* **2006**, *71*, 4585−4589.
(16) Sifniades, S. *J. Org. Chem.* **1975**, *40*, 3562−3566.
(17) Kislyi, V. P.; Laikhter, A. L.; Ugrak, B. I.; Semenov, V. V. *Russ. Chem. Bull.* **1994**, *43*, 70−74.
(18) Laikhter, A. L.; Kislyi, V. P.; Semenov, V. V. *Mendeleev Commun.* **1993**, *3*, 20−21.
(19) Nakaike, Y.; Taba, N.; Itoh, S.; Tobe, Y.; Nishiwaki, N.; Ariga, M. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 2413−2417.
(20) Hessel, V.; Kralisch, D.; Kockmann, N.; Noël, T.; Wang, Q. *ChemSusChem* **2013**, *6*, 746−789.
(21) Kulkarni, A. A. *Beilstein J. Org. Chem.* **2014**, *10*, 405−424.
(22) (a) Brocklehurst, C. E.; Lehmann, H.; La Vecchia, L. *Org. Process Res. Dev.* **2011**, *15*, 1447−1453. (b) Yu, Z.; Zhou, P.; Liu, J.; Wang, W.; Yu, C.; Su, W. *Org. Process Res. Dev.* **2016**, *20*, 199−203.
(23) See Supporting Information for details. The product yield does not depend on the duration of the stirring with desiccant, even after 3 h stirring of the reaction mixture with magnesium sulfate the yield of the reaction did not change.
(24) Yield determined by 1H NMR using mesytline as internal standard due to the volatility of the product.
(25) See Experimental Section for details
(26) Simmons, T.; Kreuz, K. *J. Org. Chem.* **1968**, *33*, 836−837.
(27) See Experimental Section for details
(28) Pinnick, H. W. In *Organic Reactions*; John Wiley & Sons, Inc., 2004.
(29) Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. *J. Org. Chem.* **1997**, *62*, 7512−7515.
(30) Zen, S.; Kaji, E. *Org. Synth.* **1977**, *57*, 60.
(31) Niyazymbetov, M. E.; Evans, D. H. *J. Org. Chem.* **1993**, *58*, 779−783.
(32) Kim, S.-U.; Liu, Y.; Nash, K. M.; Zweier, J. L.; Rockenbauer, A.; Villamena, F. A. *J. Am. Chem. Soc.* **2010**, *132*, 17157−17173.
(33) Feuer, H.; Monter, R. P. *J. Org. Chem.* **1969**, *34*, 991−995.
(34) (a) Martynov, I. V.; Zavel'skii, V. O.; Kovalenko, S. V.; Yurtanov, A. I. *Izv. Akad. Nauk SSSR, Ser. khim.* **1982**, 1029−1033. (b) Martynov, I. V.; Zavel'skii, V. O.; Kovalenko, S. V.; Fetisov, V. I.; Yurtanov, A. I. *Dokl. Akad. Nauk SSSR* **1983**, 152−156.
(35) Sin, I.; Kang, C. S.; Bandara, N.; Sun, X.; Zhong, Y.; Rogers, B. E.; Chong, H.-S. *Bioorg. Med. Chem.* **2014**, *22*, 2553−2562.
(36) Takeuchi, Y.; Itoh, N.; Koizumi, T.; Yamagami, C.; Takeuchi, Y. *Magn. Reson. Chem.* **1992**, *30*, 58−64.
(37) Paine, J. B.; Brough, J. R.; Buller, K. K.; Erikson, E. E.; Dolphin, D. *J. Org. Chem.* **1987**, *52*, 3993−3997.
(38) Sedelmeier, J.; Ley, S. V.; Baxendale, I. R.; Baumann, M. *Org. Lett.* **2010**, *12*, 3618−3621.
(39) Greene, B.; Lewis, K. *Aust. J. Chem.* **1968**, *21*, 1845−1852.
(40) Schröder, K.; Join, B.; Amali, A. J.; Junge, K.; Ribas, X.; Costas, M.; Beller, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 1425−1429.

DOI: 10.1021/acs.joc.6b01634
J. Org. Chem. 2016, 81, 9415−9421