A Straightforward Synthesis of 2-[1-Alkyl-5,6-bis(alkoxycarbonyl)-1,2,3,4-tetrahydro-2-oxopyridin-3-yl]acetic Acid Derivatives *via* Domino *Michael* Addition–Cyclization Reaction

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A new and efficient synthesis of 2-[1-alkyl-5,6-bis(alkoxycarbonyl)-1,2,3,4-tetrahydro-2-oxopyridin-3-yl]acetic acid derivatives by a one-pot three-component reaction between primary amine, dialkyl acetylenedicarboxylate, and itaconic anhydride (= 3,4-dihydro-3-methylidenefuran-2,5-dione) is reported. The reaction was performed without catalyst and under solvent-free conditions with excellent yields. Notably, the ready availability of the starting materials, and the high level of practicability of the reaction and workup make this approach an attractive complementary method to access to unknown 2-[1-alkyl-5,6-bis(alkoxycarbonyl)-1,2,3,4-tetrahydro-2-oxopyridin-3-yl]acetic acid derivatives. The structures were corroborated spectroscopically (IR, ^{1}H- and ^{13}C-NMR, and EI-MS) and by elemental analyses. A plausible mechanism for this type of domino *Michael* addition–cyclization reaction is proposed (*Scheme 2*).

1. Introduction. – Pyridine synthesis, to which a great deal of work has been devoted by chemists until recently, has long occupied a significant place in organic synthesis, resulting in the development of a wide range of synthetic methods[1]). Nevertheless, these methods suffer from many limitations such as complicated procedures, harsh reaction conditions, the requirement for a metal, and substrates that are not readily available. Consequently, it is desirable to find new, single-step, and efficient methods for the construction of pyridines. As part of our ongoing research aimed at developing metal-free, multicomponent, and diversity-oriented domino-based syntheses of biologically relevant heterocycles, here, we report a novel synthesis of 2-[1-alkyl-5,6-bis(alkoxycarbonyl)-1,2,3,4-tetrahydro-2-oxopyridin-3-yl]acetic acid derivatives.

2. Results and Discussion. – Recently, we focused our interest on the preparation of new compound libraries and synthetically nitrogenated analogs of important natural products in medicinal chemistry by using one-pot synthesis and reactions of enamines and dienamines [5]. We previously found that the reaction of secondary amines and electron-deficient acetylenic compounds with *Michael* acceptors such as arylsulfonyl

[1]) For a recent review of *de novo* methods for pyridine synthesis, see [1]. For selected recent examples on the transition metal-catalyzed synthesis of substituted pyridines, see [2]. For selected recent examples of the synthesis of substituted pyridines *via* multicomponent reactions, see [3]. For selected recent examples of the synthesis of substituted pyridines *via* using ammonium acetate as the N source, see [4].

isocyanate successfully led to polysubstituted azetidine-2,4-diones [6] and maleimides [7] (*Scheme 1*). Along the same lines, we were interested in the reaction of a primary amine **1**, dialkyl acetylenedicarboxylates **2**, and itaconic anhydride (= 3,4-dihydro-3-methylidenefuran-2,5-dione). To the best of our knowledge, there has been no report on the reaction of enamines (derived from acetylenic compounds) with itaconic anydride. Under this aspect, we report here a straightforward approach to 2-[1-alkyl-5,6-bis(alkoxycarbonyl)-1,2,3,4-tetrahydro-2-oxopyridin-3-yl]acetic acid derivatives *via* a one-pot process. As compiled in the *Table*, the one-pot, optimized equimolar reaction of primary amines **1**, dialkyl acetylenedicarboxylates **2**, and itaconic anhydride proceeded smoothly under solvent-free conditions to afford 2-[1-alkyl-5,6-bis(alkoxycarbonyl)-1,2,3,4-tetrahydro-2-oxopyridin-3-yl]acetic acid derivatives **3** after 5 h in 70–87% yields (*Table*).

Scheme 1. *Synthesis of Azetidine-2,4-diones and Maleimides* via *Enamine as the Key Intermediate*

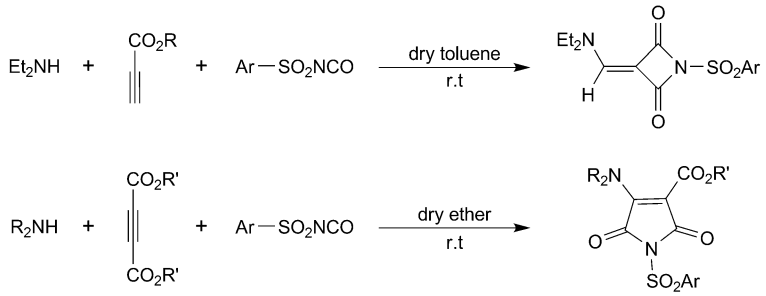
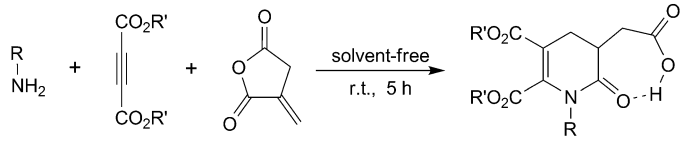


Table. *Single-Step Synthesis of 2-[1-Alkyl-5,6-bis(alkoxycarbonyl)-1,2,3,4-tetrahydro-2-oxopyridin-3-yl]-acetic Acid Derivatives*



1 **2** **3**

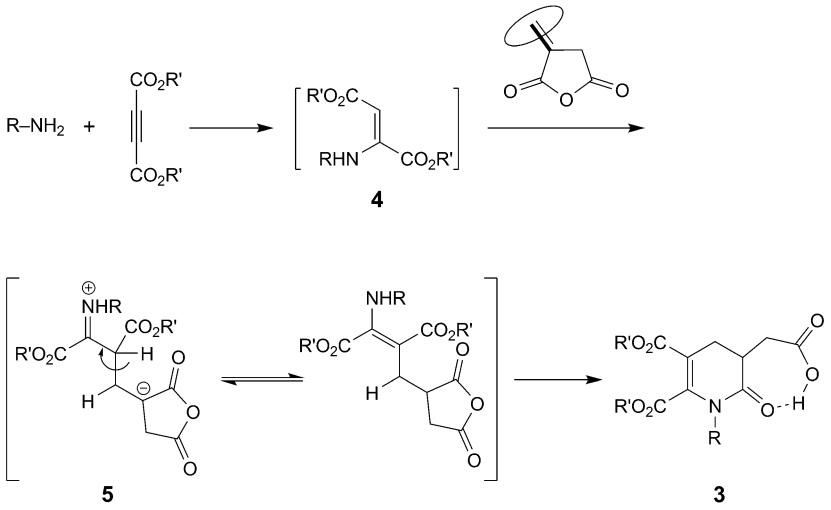
Entry	Products **3**	R	R′	Yield [%]
1	**3a**	Pr	Me	82
2	**3b**	Pr	Et	76
3	**3c**	Bu	Me	73
4	**3d**	^{i}Bu	Et	87
5	**3e**	^{i}Bu	Me	72
6	**3f**	^{i}Bu	Et	78
7	**3g**	Bn	Me	70
8	**3h**	4-Me–$C_6H_4CH_2$	Me	81
9	**3i**	4-MeO–$C_6H_4CH_2$	Me	86

The structures of compounds **3a**–**3i** were deduced from their elemental analysis, and IR, high-field ^{1}H- and ^{13}C-NMR, and mass spectra. For example, the mass spectrum of **3d** displayed the M^+ peak at m/z 355, which is in agreement with the proposed

structure. The IR spectrum of **3d** in KBr showed an absorption band due to the OH stretching frequency at 3210 cm^{-1}. Further absorption bands at 1727, 1700, and 1631 cm^{-1} are due to the C=O groups. The ^{1}H-NMR spectrum of **3d** exhibited three *triplet*s for Me groups (δ(H) 0.76 (*t*, *J* = 7.3), 1.15 (*t*, *J* = 7.1), and 1.24 (*t*, *J* = 7.2)), eight *multiplet*s for seven CH_2 and one CH groups, because these H-atoms are diastereotopic (δ(H) 1.37 – 1.45, 2.28 – 2.42, 2.73 – 2.79, 2.84 – 2.89, 3.07 – 3.13, 3.58 – 3.64, 4.04 – 4.10, and 4.18 – 4.28), and one *singlet* for a OH group (δ(H) 9.20). The ^{1}H-decoupled ^{13}C-NMR spectrum of **3d** showed 17 distinct resonances in agreement with the suggested structure.

Based on these results, a plausible mechanism for the sequential three-component reaction is proposed (*Scheme 2*). In the first step, the formation of enamine **4** occurs through addition of amine **1** to active acetylenic compound **2**. Next, *Michael* addition of **4** to the C=C bond of itaconic anhydride produces the nonisolable zwitterionic adduct, intermediate **5**, that promptly afforded 2-[1-alkyl-5,6-bis(alkoxycarbonyl)-1,2,3,4-tetrahydro-2-oxopyridin-3-yl]acetic acid derivatives **3** by an intramolecular azacyclization *via* tautomerization CH/NH or 1,3-H shift and intramolecular nucleophilic attack of the N–H bond of enamine across the C=O bond (*Scheme 2*).

Scheme 2. *Mechanistic Proposal for the Synthesis of 2-[1-Alkyl-5,6-bis(alkoxycarbonyl)-1,2,3,4-tetrahydro-2-oxopyridin-3-yl]acetic Acid Derivatives* **3a** – **3i**



In summary, we have reported a novel, efficient, and practical one-pot procedure for the preparation of 2-[1-alkyl-5,6-bis(alkoxycarbonyl)-1,2,3,4-tetrahydro-2-oxopyridin-3-yl]acetic acid derivatives by a unique one-pot three-component reaction of primary amines, dialkyl acetylenedicarboxylates, and itaconic anhydride. This method circumvents some of the problems and limitations associated with frequently used procedures; it is advantageous in terms of simplicity and mildness, and hopefully could find wide application in the synthesis of complex pyridine-containing compounds. Notably, this environmentally friendly single-flask approach avoids transition-metal catalysts and organic solvents, employs readily available materials, and occurs with

complete control of pathway selectivity. Current studies to extend this methodology, including the use of other nucleophilic partners, are in progress.

Experimental Part

General. The primary amines, dimetyl, and diethyl acetylenedicarboxylate, and itaconic anhydride were obtained from *Merck* (Germany) and *Fluka* (Switzerland), and were used without further purification. M.p.: *Electrothermal 9100* apparatus. IR Spectra: in KBr on a *Shimadzu IR-460* spectrometer. ^{1}H- and ^{13}C-NMR spectra: at 500 and 125 MHz, resp., on a *BRUKER DRX 500-AVANCE* FT-NMR instrument, in $CDCl_3$ if not otherwise stated. MS: *FINNIGAN-MATT* 8430 mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses for C, H and N: *Heraeus CHN–O–Rapid* analyzer.

General Procedure (exemplified for **3a**). To a magnetically stirred 5-ml flat-bottom flask containing $PrNH_2$ (0.059 g, 1 mmol) was added dimethyl acetylenedicarboxylate (0.142 g, 1 mmol), and itaconic anhydride (0.112 g, 1 mmol). The resulting mixture was stirred for 5 h at ambient temp. After completion of the reaction (the progress of the reaction was followed by TLC (hexane/AcOEt, 7:1)), the crude product was purified by column chromatography (CC; SiO_2 (*Merck*; 230–240 mesh); hexane/AcOEt 7:1).

2-[1,2,3,4-Tetrahydro-5,6-bis(methoxycarbonyl)-2-oxo-1-propylpyridin-3-yl]acetic Acid (**3a**). Yield: 256 mg (82%). Yellow oil. IR: 3331 (OH), 1730, 1742 (COOMe), 1659 (CO), 1288 (C–N), 1124 (C–O). ^{1}H-NMR: 0.75 (*t*, *J* = 7.4, 3 H); 1.43–1.50 (*m*, 2 H); 2.31–2.45 (*m*, 2 H); 2.76–2.82 (*m*, 2 H); 2.87–2.93 (*m*, 1 H); 3.05–3.11 (*m*, 1 H); 3.56–3.62 (*m*, 1 H); 3.65 (*s*, 3 H); 3.81 (*s*, 3 H); 10.13 (br., 1 H). ^{13}C-NMR: 10.4; 20.1; 24.8; 33.7; 35.5; 44.0; 51.6; 52.5; 106.7; 142.7; 163.4; 165.0; 170.2; 176.5. EI-MS (70 eV): 313 (4, M^+), 282 (20), 254 (94), 180 (100), 112 (36), 80 (35), 55 (47). Anal. calc. for $C_{14}H_{19}NO_7$ (313.30): C 53.67, H 6.11, N 4.47; found: C 53.68, H 6.09, N 4.45.

2-[1,2,3,4-Tetrahydro-5,6-bis(ethoxycarbonyl)-2-oxo-1-propylpyridin-3-yl]acetic Acid (**3b**). Yield: 259 mg (76%). Yellow oil. IR: 3210 (OH), 1722, 1703 (COOEt), 1632 (CO), 1280 (C–N), 1132 (C–O). ^{1}H-NMR: 0.84 (*t*, *J* = 7.2, 3 H); 1.27 (*t*, *J* = 7.1, 3 H); 1.35 (*t*, *J* = 7.1, 3 H); 1.48–1.61 (*m*, 2 H); 2.37–2.52 (*m*, 2 H); 2.82–2.89 (*m*, 2 H); 2.93–3.01 (*m*, 1 H); 3.13–3.19 (*m*, 1 H); 3.63–3.71 (*m*, 1 H); 4.15–4.20 (*m*, 2 H); 4.28–4.41 (*m*, 2 H); 9.50 (br., 1 H). ^{13}C-NMR: 10.8; 13.4; 13.5; 21.8; 25.2; 39.9; 35.6; 46.0; 60.6; 61.5; 107.0; 142.7; 162.9; 164.5; 170.4; 176.3. EI-MS (70 eV): 341 (5, M^+), 324 (2), 296 (17), 282 (100), 266 (32), 248 (19), 208 (30), 194 (44), 166 (58). Anal. calc. for $C_{16}H_{23}NO_7$ (341.36): C 56.30, H 6.79, N 4.10; found: C 56.31, H 6.77, N 4.09.

2-[1-Butyl-1,2,3,4-tetrahydro-5,6-bis(methoxycarbonyl)-2-oxopyridin-3-yl]acetic Acid (**3c**). Yield: 239 mg (73%). Yellow oil. IR: 3280 (OH), 1708, 1722 (COOMe), 1673 (CO), 1258 (C–N), 1135 (C–O). ^{1}H-NMR: 0.88 (*t*, *J* = 7.30, 3 H); 1.29–1.49 (*m*, 4 H); 2.39–2.53 (*m*, 2 H); 2.81–3.06 (*m*, 3 H); 3.16–3.24 (*m*, 1 H); 3.41–3.47 (*m*, 1 H); 3.74 (*s*, 3 H); 3.90 (*s*, 3 H); 9.91 (br., 1 H). ^{13}C-NMR: 13.6; 20.0; 25.6; 30.6; 34.3; 36.1; 45.0; 52.2; 53.0; 107.2; 143.3; 163.9; 165.4; 170.7; 176.5. EI-MS (70 eV): 327 (3, M^+), 296 (9), 268 (47), 220 (25), 180 (54), 85 (30), 59 (100). Anal. calc. for $C_{15}H_{21}NO_7$ (327.33): C 55.04, H 6.47, N 4.28; found: C 53.68, H 6.09, N 4.45.

2-[1-Butyl-1,2,3,4-tetrahydro-5,6-bis(ethoxycarbonyl)-2-oxopyridin-3-yl]acetic Acid (**3d**). Yield: 309 mg (87%). Yellow oil. IR: 3210 (OH), 1727, 1720 (COOEt), 1631 (CO), 1265 (C–N), 1132 (C–O). ^{1}H-NMR: 0.76 (*t*, *J* = 7.30, 3 H); 1.15 (*t*, *J* = 7.1, 3 H) 1.24 (*t*, *J* = 7.1, 3 H); 1.37–1.45 (*m*, 4 H); 2.28–2.42 (*m*, 2 H); 2.73–2.79 (*m*, 2 H); 2.84–2.89 (*m*, 1 H); 3.07–3.13 (*m*, 1 H); 3.58–3.64 (*m*, 1 H); 4.04–4.10 (*m*, 2 H); 4.18–4.28 (*m*, 2 H); 9.20 (br., 1 H). ^{13}C-NMR: 13.4; 13.6; 13.9; 19.7; 25.5; 28.9; 34.1; 36.0; 44.6; 61.0; 62.3; 107.4; 152.9; 163.3; 164.9; 170.7; 176.2. EI-MS (70 eV): 355 (5, M^+), 296 (100), 194 (41), 166 (42), 83 (42). Anal. calc. for $C_{17}H_{25}NO_7$ (355.38): C 57.45, H 7.09, N 3.94; found: C 57.44, H 7.11, N 3.92.

2-[1,2,3,4-Tetrahydro-5,6-bis(methoxycarbonyl)-1-(2-methylpropyl)-2-oxopyridin-3-yl]acetic Acid (**3e**). Yield: 235 mg (72%). Yellow oil. IR: 3370 (OH), 1732, 1729 (COOMe), 1632 (CO), 1270 (C–N), 1136 (C–O). ^{1}H-NMR: 0.84 (*d*, *J* = 7.1, 6 H); 1.91–2.02 (*m*, 1 H); 2.42–2.47 (*m*, 2 H); 2.81–2.99 (*m*, 3 H); 3.03–3.08 (*m*, 1 H); 3.65–3.3.70 (*m*, 1 H); 3.65 (*s*, 3 H); 3.81 (*s*, 3 H); 10.13 (br., 1 H).

^{13}C-NMR: 19.25; 19.30; 25.1; 27.7; 34.8; 36.2; 50.7; 51.5; 52.5; 107.7; 142.9; 163.3; 165.0; 170.8; 175.7. EI-MS (70 eV): 327 (5, M^+), 296 (19), 268 (87), 252 (30), 224 (18), 180 (100), 152 (16), 84 (17), 55 (35). Anal. calc. for $C_{15}H_{21}NO_7$ (327.33): C 55.04, H 6.47, N 4.28; found: C 55.02, H 6.48, N 4.25.

2-[1,2,3,4-Tetrahydro-5,6-bis(ethoxycarbonyl)-1-(2-methylpropyl)-2-oxopyridin-3-yl]acetic Acid (**3f**). Yield: 277 mg (78%). Yellow oil. IR: 3281 (OH), 1720, 1709 (COOEt), 1632 (CO), 1289 (C–N), 1211 (C–O). ^{1}H-NMR: 0.83 (*t*, *J* = 7.3, 6 H); 1.26 (*t*, *J* = 7.0, 3 H) 1.39 (*t*, *J* = 7.0, 3 H); 1.92 – 1.97 (*m*, 1 H); 2.40 – 2.55 (*m*, 2 H); 2.79 – 2.89 (*m*, 3 H); 3.63 – 3.69 (*m*, 1 H); 3.71 – 3.78 (*m*, 1 H); 4.15 – 4.20 (*m*, 2 H); 4.29 – 4.39 (*m*, 2 H); 8.24 (br., 1 H). ^{13}C-NMR: 13.4; 13.6; 19.2; 19.3; 25.1; 27.7; 34.1; 35.9; 50.8; 60.7; 61.9; 107.9; 142.9; 162.8; 164.5; 170.9; 176.2. EI-MS (70 eV): 355 (5, M^+), 310 (16), 296 (100), 280 (29), 238 (37), 194 (74), 166 (47), 113 (44), 85 (51). Anal. calc. for $C_{17}H_{25}NO_7$ (355.38): C 57.45, H 7.09, N 3.94; found: C 57.47, H 7.10, N 3.95.

2-[1-Benzyl-1,2,3,4-tetrahydro-5,6-bis(methoxycarbonyl)-2-oxopyridin-3-yl]acetic Acid (**3g**). Yield: 252 mg (70%). Yellow oil. IR: 3290 (OH), 1724, 1703 (COOMe), 1633 (CO), 1271 (C–N), 1187 (C–O). ^{1}H-NMR: 2.41 – 2.51 (*m*, 2 H); 2.83 – 2.86 (*m*, 2 H); 2.97 – 3.08 (*m*, 1 H); 3.55 (*s*, 3 H); 3.62 (*s*, 3 H); 4.52 (*d*, ^2J = 16.0, 1 H); 4.91 (*d*, ^2J = 16.0, 1 H); 7.08 – 7.22 (*m*, 5 H); 8.50 (br., 1 H). ^{13}C-NMR: 25.4; 34.1; 36.0; 47.2; 52.1; 52.7; 108.4; 127.0; 127.5; 128.4; 136.3; 142.5; 163.7; 165.4; 171.1; 176.0. EI-MS (70 eV): 361 (2, M^+), 230 (7), 302 (41), 238 (25), 105 (60), 91 (100), 57 (52). Anal. calc. for $C_{18}H_{19}NO_7$ (361.35): C 59.83, H 5.30, N 3.88; found: C 59.81, H 5.31, N 3.76.

2-[1,2,3,4-Tetrahydro-5,6-bis(methoxycarbonyl)-1-(4-methylbenzyl)-2-oxopyridin-3-yl]acetic Acid (**3h**). Yield: 304 mg (81%). Yellow oil. IR: 3310 (OH), 1721, 1712 (COOMe), 1632 (CO), 1269 (C–N), 1156 (C–O). ^{1}H-NMR: 2.29 (*s*, 3 H); 2.44 – 2.55 (*m*, 2 H); 2.86 – 2.95 (*m*, 2 H); 3.03 – 3.07 (*m*, 1 H); 3.67 (*s*, 3 H); 3.71 (*s*, 3 H); 4.51 (*d*, ^2J = 15.7, 1 H); 4.93 (*d*, ^2J = 15.7, 1 H); 7.04 – 7.12 (*m*, 4 H); 8.35 (br., 1 H). ^{13}C-NMR: 21.1; 25.5; 36.1; 37.1; 47.2; 52.1; 52.8; 108.3; 127.1; 129.1; 133.3; 137.2; 142.7; 163.7; 165.4; 171.0; 176.5. EI-MS (70 eV): 375 (1, M^+), 296 (2), 238 (2), 113 (7), 83 (100). Anal. calc. for $C_{19}H_{21}NO_7$ (375.37): C 60.79, H 5.64, N 3.73; found: C 60.78, H 5.65, N 3.72.

2-[1,2,3,4-Tetrahydro-1-(4-methoxybenzyl)-5,6-bis(methoxycarbonyl)-2-oxopyridin-3-yl]acetic Acid (**3i**). Yield: 336 mg (86%). Yellow oil. IR: 3428 (OH), 1722, 1715 (COOMe), 1634 (CO), 1269 (C–N), 1168 (C–O). ^{1}H-NMR: 2.41 – 2.51 (*m*, 2 H); 2.83 – 2.85 (*m,* 2 H); 2.95 – 3.05 (*m*, 1 H); 3.57 (*s*, 3 H); 3.61 (*s*, 3 H); 3.64 (*s*, 3 H); 4.47 (*d*, ^2J = 15.5, 1 H); 4.90 (*d*, ^2J = 15.5, 1 H); 7.00 – 7.08 (*m*, 4 H); 9.34 (br., 1 H). ^{13}C-NMR: 25.5; 34.1; 36.0; 47.1; 52.1; 52.7; 60.4; 108.4; 127.1; 129.1; 137.1; 142.6; 159.1; 163.7; 165.4; 171.0; 176.0. EI-MS (70 eV): 391 (1, M^+), 344 (9), 316 (51), 296 (43), 238 (52), 194 (30), 105 (100), 69 (62). Anal. calc. for $C_{19}H_{21}NO_8$ (391.37): C 58.31, H, 5.41, N 3.58. found: C 58.33, H 5.38, N 3.57.

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