# A New Synthesis of (*E*)-4-Alkoxy-2-formylamino-3-butenoic Acid Derivatives Utilizing 3-Alkoxy-1-isocyano-1-lithiopropenes

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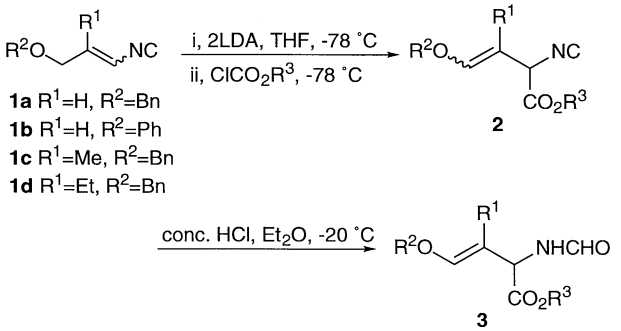
The title amino acid derivatives have been prepared in two steps from 3-alkoxy-1-isocyanopropenes. The key step is the alkoxycarbonylation of 3-alkoxy-1-isocyano-1-lithiopropenes with alkyl chloroformates to afford the corresponding 4-alkoxy-2-isocyano-3-butenoates, which are readily converted to the title compounds by acidic hydrolysis.

Some members of (*E*)-4-alkoxy-2-amino-3-butenoic acids have been found in nature,[1] and have attracted much attention because of their potential use as inhibitors of several important enzymes.[2] Although a few methods for the synthesis of this class of compounds have been reported,[3] these methods have started from inaccessible materials and involved either multi-steps or incomplete stereoselectivity. The only previous general synthesis was recorded by Hoppe and Schoellkopf.[3c] However, it can not be applied to the preparation of the derivatives carrying a substituent at the 3-position, which are also of interest because of their potential biological activities. Therefore, any new general route to the 3-substituted derivatives is of value. In a previous paper,[4] we have demonstrated that treatment of 3-benzyloxy-1-isocyanopropenes **1a** and **1c** with lithium diisopropylamide (LDA) afforded the corresponding 3-benzyloxy-1-isocyano-1-lithiopropenes, which can serve as 3-hydroxypropanoyl anion equivalents via alkylation with alkyl halides, followed by sequential hydrolysis and hydrogenolysis. As part of our program to explore synthetic utility and potential of these lithium products we have investigated the possibility of their use in the preparation of (*E*)-4-alkoxy-2-amino-3-butenoic acid derivatives. In this paper we wish to report the results of our studies, which offer a general route to this class of compounds including the 3-substituted derivatives.




**Scheme 1.**

The key reaction in our sequence is regioselective alkoxycarbonylation of 3-alkoxy-1-isocyanopropenes **1**[5,6] with alkyl chloroformates to afford 4-alkoxy-2-isocyano-3-butenoates **2**. As outlined in Scheme 1, treatment of **1** with 2 equivalents of LDA generated 3-alkoxy-1-isocyano-1-lithiopropenes, which were allowed to react with one equivalent of alkyl chloroformates to afford the isocyano esters **2**.[5,7] Each of the products was isolated as a yellow liquid by purification using preparative TLC on $SiO_2$ and uniformly exhibits IR absorptions at ca. 2145 and 1755 $cm^{-1}$, which indicates that both of the isocyano and alkoxycarbonyl groups are not conjugated with the vinyl moiety. The production of **2** can be interpreted as follows. Alkoxycarbonylation of the lithiated isocyanopropenes with alkyl chloroformates gives the initial alkoxycarbonylation products, 4-alkoxy-2-isocyano-2-butenoates. The migration of the double bond proceeds with the help of an additional molar of LDA; deprotonation of a proton at the 4-position of the initial products affords the corresponding dienolate anions,[8] which are exclusively trapped with a proton at the 2-position to produce **2**. The results using four isocyanopropenes **1** and three chloroformates are summarized in Table 1. Isolated yields ranged from 22 to 96%. Compounds **2a** and **2b** proved to be rather unstable under the purification conditions; although the $^1H$ NMR spectra of the crude products revealed that they were both produced quantitatively, their separation using preparative TLC afforded only rather poor results (Entries 1 and 2, respectively). Their instability is probably provided by the absence of a substituent at the 3-position. So the crude products were used in the next step without any purification only in the cases of **2a** and **2b**. Compounds **2c-f** were readily isolated by preparative TLC, and the isolated yields were good (Entries 3-6, respectively). It can be reasonably assumed that the *E*-isomer was exclusively (**2a**, **2b**, and **2f**) or predominantly (**2c-e**) formed in each case in view of the thermodynamic stability. The *E*-configuration of the major isomer of **2e** was unambiguously confirmed on the basis of a NOE experiment. Thus, irradiation of the signal at $\delta_H$ 4.57 due to 2-H resulted in an 11% enhancement of the signal at $\delta_H$

**Table 1.** Preparation of (*E*)-4-alkoxy-2-amino-3-butenic acid derivatives **3**

| Entry | **1** (*E*/*Z*)[a] | $R^3$ | **2** (Yield/%)[b] | *E*/*Z*[a] | **3** (Yield/%)[b] |
|---|---|---|---|---|---|
| 1 | **1a** (~50:50) | Et | **2a** (quant)[a,c,d] | ~100:0 | **3a** (57)[g] |
| 2 | **1b** (~60:40) | Et | **2b** (quant)[a,c,e] | ~100:0 | **3b** (53)[h] |
| 3 | **1c** (~60:40) | Et | **2c** (64) | ~80:20[f] | **3c** (62) |
| 4 | **1d** (~65:35) | Me | **2d** (96) | ~80:20[f] | **3d** (69) |
| 5 | **1d** | Et | **2e** (84) | ~80:20[f] | **3e** (66) |
| 6 | **1d** | Bn | **2f** (62) | ~100:0 | **3f** (60) |

[a]Determined by $^1H$ NMR spectrum. [b]Isolated yields unless stated otherwise. [c]Used without purification in the next step. [d]Isolated yield was 24%. [e]Isolated yield was 22%. [f]Inseparable by preparative TLC on $SiO_2$. [g]Overall yield from **1a**. [h]Overall yield from **1b**.

6.31 due to 4-H, while no NOE was observed between the signals due to 4-H and 2-H of the minor isomer.

Hydrolysis of the isocyano esters **2** was carried out with concentrated hydrochloric acid in diethyl ether at -20 °C. Competition of the enol ether function with the isocyano group to be hydrolyzed could be suppressed effectively by carrying hydrolysis at this low temperature, and the corresponding (*E*)-4-alkoxy-2-formylamino-3-butenoic acid esters **3** were obtained in satisfactory yields with high stereoselectivity.[5,9] The results are also shown in Table 1. The yields of **3a** and **3b** refer to overall yields from the isocyanopropenes **1a** and **1b**, respectively. Stereochemical proof of these products was facilitated by $^1$H NMR. Thus, the *E*-configuration of **3a** and **3b** was clear from analysis of the coupling constants ($J_{3H\text{-}4H}$=12.3 Hz each), which were almost equal to those of the related compounds, methyl (*E*)-2-acetylamino-4-methoxy-3-butenoate reported by Keith and his co-workers ($J_{3H\text{-}4H}$=13 Hz)[3a] and ethyl (*E*)-2-formylamino-4-methoxy-3-butenoate reported by Hoppe and Schoellkopf ($J_{3H\text{-}4H}$=12 Hz),[3c] and far from that of methyl (*Z*)-2-acetylamino-4-methoxy-3-butenoate ($J_{3H\text{-}4H}$=7 Hz).[3a] The *E*-configuration of **3c-f** can be inferred from the values of chemical shifts of the C(2) and C(4) protons ($\delta_{2H}$ 4.98-5.04; $\delta_{4H}$ 6.22-6.34), when comparisons are made with those of methyl (*E*)- and (*Z*)-2-acetylamino-4-methoxy-3-butenoates ($\delta_{2H}$ 4.8 and $\delta_{4H}$ 6.64 for *E*, $\delta_{2H}$ 4.5 and $\delta_{4H}$ 6.10 for *Z*)[3a] taking the effect of the 3-alkyl substituent into consideration. The *E*-configuration of **3e** was unambiguously confirmed on the basis of a NOE experiment. Thus, irradiation of the signal at $\delta_H$ 4.98 due to 2-H resulted in a 7.8% enhancement of the signal at $\delta_H$ 6.29 due to 4-H. We assume that the acid-catalyzed isomerization of the *Z*-isomer to the *E*-isomer took place during the hydrolysis.

The present two-step preparation of (*E*)-4-alkoxy-2-formylamino-3-butenoates, utilizing 3-alkoxy-1-isocyanopropenes may find some value in synthesis. We are actively applying this methodology to the synthesis of more complex systems containing this structural array and analogues thereof.

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## References and Notes


1 For example, see L. D. Owens, J. F. Thompson, R. G. Pitcher, and T. Williams, *J. Chem. Soc., Chem. Commun.*, **1972**, 714; D. L. Pruess, J. P.Scannell, T. C. Demny, L. H. Sello, T. Williams, and A. Steempel, *J. Antibiot.*, **25**, 122 (1972); U. Sahm, G. Knoblochi, and F. Wagner, *J. Antibiot.*, **26**, 389 (1973).

2 M. J. Tisdale, *Biochem. Pharmacol.*, **29**, 501 (1980); T. Dashman, *Life Sci.*, **27**, 1415 (1980); S. B. Smith and R. A. Freedland, *Arch. Biochem. Biophys.*, **209**, 335 (1981); J. R. Sufrin, J. B. Lombardini, and D. D. Keith, *Biochem. Biophys. Res. Commun.*, **106**, 251 (1982), and references therein.

3 a) D. D. Keith, J. A. Tortora, and R. Yang, *J. Org. Chem.*, **43**, 3711 (1978); b) D. D. Keith, R. Yang, J. A. Tortora, and M. Weigele, *J. Org. Chem.*, **43**, 3713 (1978); c) I. Hoppe and U. Schoellkopf, *Synthesis*, **1982**, 129.

4 K. Kobayashi, H. Akamatsu, K. Takada, O. Morikawa, and H. Konishi, *Tetrahedron Lett.*, **37**, 2437 (1996).

5 All of the new products described in this paper gave satisfactory analytical results (HR MS for **1** and **2**, and elemental analyses for **3**).

6 Compounds **1a**,[4] **1b**, **1c**,[4] and **1d** were prepared according to the procedure reported by us.[4] **1b**: *E*:*Z*=~60:40; bp 170 °C (bath temp)/0.1 Torr; ν/cm$^{-1}$ (neat) 2130, 1649; $\delta_H$ (60 MHz, $CCl_4$) 4.48 (1.2H, d, *J*=3.6 Hz), 4.75 (0.8H, d, *J*=4.0 Hz), 5.7-6.3 (2H, m), 6.65-7.35 (5H, m); *m/z* (%) 159 (M$^+$, 38), 130 (99), 65 (100). **1d**: *E*:*Z*=~65:35; bp 180 °C (bath temp)/0.1 Torr; ν/cm$^{-1}$ (neat) 2124; $\delta_H$ (60 MHz, $CCl_4$) 1.06 (3H, t, *J*=7.2 Hz), 2.0-2.4 (2H, m), 3.95 (0.7H, s), 4.22 (1.3H, s), 4.50 (2H, s), 5.55-5.65 (0.65H, m), 5.75-5.85 (0.35H, m), 7.26 (5H, s); *m/z* (%) 201 (M$^+$, 3.2), 172 (30), 107 (69), 91 (100).

7 Spectral [IR (neat), $^1$H NMR (270 MHz, $CDCl_3$), and MS] data for **2**; **2a:** ν/cm$^{-1}$ 2145, 1754, 1682; $\delta_H$ 1.31 (3H, t, *J*=7.3 Hz), 4.26 (2H, q, *J*=7.3 Hz), 4.69 (1H, d, *J*=8.0 Hz), 4.84 (2H, s), 5.01(1H, dd, *J*=12.3, 8.0 Hz), 6.76 (1H, d, *J*=12.3 Hz), 7.3-7.4 (5H, m); *m/z* (%) 245 (M$^+$, 4.6), 244 (20), 91 (100). **2b**: ν/cm$^{-1}$ 2143, 1759, 1674; $\delta_H$ 1.34 (3H, t, *J*=7.3 Hz), 4.30 (2H, q, *J*=7.3 Hz), 4.82 (1H, d, *J*=7.6 Hz), 5.40 (1H, dd, *J*=12.0, 7.6 Hz), 6.93 (1H, d, *J*=12.0 Hz), 7.03 (2H, t, *J*=7.6 Hz), 7.23 (1H, t, *J*=7.6 Hz), 7.35 (2H, t, *J*=7.6 Hz); *m/z* (%) 231 (M$^+$, 42), 146 (100). **2c**: (*E*:*Z*=~80:20); ν/cm$^{-1}$ 2144, 1752, 1682; $\delta_H$ 1.24 and 1.28 (3H, 2t, *J*=7.1 Hz each), 1.59 (0.6H, s), 1.72 (2.4H, s), 4.23 (2H, q, *J*=7.1 Hz), 4.57 (0.8H, s), 4.84 (0.2H, s), 4.87 (2H, s), 6.33 (0.8H, s), 6.44 (0.2H, s), 7.3-7.4 (5H, m); *m/z* (%) 259 (M$^+$, 21), 91 (100). **2d**: (*E*:*Z*=~80:20); ν/cm$^{-1}$ 2145, 1756, 1675; $\delta_H$ 1.00 (3H, t, *J*=7.2 Hz), 2.18 (2H, q, *J*=7.2 Hz), 3.73 (3H, s), 4.53 (0.8 H, s), 4.83 (2H, s), 4.87 (0.2 H, s), 6.27 (0.8H, s), 6.37 (0.2H, s), 7.27 (5H, s); *m/z* (%) 259 (M$^+$, 19), 91 (100). **2e**: (*E*:*Z*=~80:20); ν/cm$^{-1}$ 2144, 1753, 1675; $\delta_H$ 1.03 and 1.05 (3H, 2t, *J*=7.6 Hz each), 1.27 and 1.29 (3H, 2t, *J*=7.3 Hz each), 2.1-2.3 (2H, m), 4.23 and 4.28 (2H, 2q, *J*=7.3 Hz each), 4.57 (0.8H, s), 4.87 (2H, s), 4.89 (0.2H, s), 6.31 (0.8H, s), 6.42 (0.2H, s), 7.25-7.4 (5H, m); *m/z* (%) 273 (M$^+$, 14) 107 (18), 91 (100). **2f**: ν/cm$^{-1}$ 2144, 1754, 1675; $\delta_H$ 0.98 (3H, t, *J*=7.4 Hz), 2.1-2.25 (2H, m), 4.62 (1H, s), 4.83 (2H, s), 5.18 (1H, d, *J*=12.1 Hz), 5.19 (1H, d, *J*=12.1 Hz), 6.28 (1H, s), 7.25-7.4 (10H, m); *m/z* (%) 335 (M$^+$, 31), 244 (54), 91 (100).

8 J. C. Stowell, "Carbanions in Organic Synthesis," John Wiley & Sons, New York (1979), Chap. 6.

9 Spectral [IR (neat), $^1$H NMR (270 MHz, $CDCl_3$), and MS] data for **3**; **3a**: ν/cm$^{-1}$ 3302, 1740, 1666; $\delta_H$ 1.11 (3H, t, *J*=6.9 Hz), 4.1-4.25 (2H, m), 4.68 (2H, s), 4.75 (1H, dd, *J*=12.3, 8.3 Hz), 4.98 (1H, dd, *J*=8.3, 7.6 Hz), 6.20 (1H, br. s), 6.63 (1H, d, *J*=12.3 Hz), 7.25-7.3 (5H, m), 8.11 (1H, s); *m/z* 263 (M$^+$, 0.10), 190 (6.1), 172 (19), 91 (100). **3b**: ν/cm$^{-1}$ 3300, 1740, 1671; $\delta_H$ 1.31 (3H, t, *J*=7.3 Hz), 4.26 (2H, q, *J*=7.3 Hz), 5.16 (1H, dd, *J*=8.3, 7.6 Hz), 5.29 (1H, dd, *J*=12.3, 8.3 Hz), 6.31 (1H, br. s), 6.84 (1H, d, *J*=12.3 Hz), 6.99 (2H, d, *J*=7.6 Hz), 7.09 (1H, t, *J*=7.6 Hz), 7.33 (2H, t, *J*=7.6 Hz), 8.09 (1H, s); *m/z* (%) 249 (M$^+$, 8.5), 248 (51), 220 (62), 146 (100). **3c**: ν/cm$^{-1}$ 3294, 1738, 1680; $\delta_H$ 1.09 (3H, t, *J*=7.2 Hz), 1.57 (3H, s), 4.18 (2H, q, *J*=7.2 Hz), 4.85 (2H, s), 4.98 (1H, d, *J*=7.6 Hz), 6.34 (1H, br. s), 6.6-6.9 (1H, br), 7.29 (5H, s), 8.09 (1H, s); *m/z* (%) 277 (M$^+$, 0.06), 276 (0.39), 249 (3.5), 221 (8.7), 189 (10), 91 (100). **3d**: ν/cm$^{-1}$ 3304, 1744, 1672; $\delta_H$ 0.97 (3H, t, *J*=7.6 Hz), 2.05-2.15 (2H, m), 3.72 (3H, s), 4.83 (2H, s), 5.00 (1H, d, *J*=7.6 Hz), 6.29 (combined 2H, s and br. s), 7.3-7.35 (5H, m), 8.18 (1H, s); *m/z* (%) 277 (M$^+$, 0.05), 218 (2.6), 186 (32), 91 (100). **3e**: ν/cm$^{-1}$ 3312, 1738, 1679; $\delta_H$ 0.99 (3H, t, *J*=7.6 Hz), 1.24 (3H, t, *J*=7.3 Hz), 2.05-2.15 (2H, m), 4.18 (2H, q, *J*=7.3 Hz), 4.84 (2H, s), 4.98 (1H, d, *J*=7.6 Hz), 6.26 (1H, br. s), 6.29 (1H, s), 7.25-7.4 (5H, m), 8.18 (1H, s); *m/z* (%) 291 (M$^+$, 0.21), 218 (12), 200 (45), 91 (100). **3f**: ν/cm$^{-1}$ 3294, 1741, 1673; $\delta_H$ 0.94 (3H, t, *J*=7.6 Hz), 2.05-2.15 (2H, m), 4.75 and 4.76 (combined 2H, 2d, *J*=12.7 Hz each), 5.04 (1H, d, *J*=7.6 Hz), 5.14 (2H, s), 6.22 (combined 2H, s and br. s), 7.25-7.35 (10H, m), 8.17 (1H, s); *m/z* (%) 353 (M$^+$, 0.01), 262 (3.3), 91 (100).