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1,3-Dipolar cycloaddition reactions of ester-stabilized azomethine ylides with acrolein: a one-pot regio- and stereoselective synthesis of *N*-substituted 4-formyl-5-vinyl proline carboxylates

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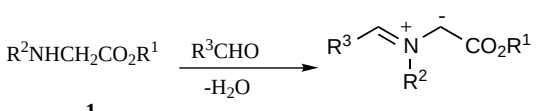
Abstract—Reaction of *N*-alkylated glycine esters with excess acrolein in the presence of acid, followed by treatment with triethylamine, provided *N*-substituted 4-formyl-5-vinyl proline carboxylates in good yields with high regio- and stereoselectivity.

The 1,3-dipolar cycloaddition reaction is one of the most efficient and widely used methods for the synthesis of nitrogen-containing five-membered heterocycles.[1] In particular, azomethine ylides have been used to synthesize pyrrolidines with various substitutions, allowing the introduction of several functional groups in a single operation. Ester-stabilized azomethine ylides (**2**), typically generated in situ via ring-opening of acyl aziridines[2] or reaction of glycine esters (**1**) with a carbonyl compound[3] (Scheme 1), undergo a [3+2] dipolar addition reaction with various dipolarophiles and provide ready access to proline carboxylates. However, when an aliphatic aldehyde containing an α-proton ($R^3 = RCH_2$-) is utilized, the resulting ylide (**2**) can tautomerize to an enamine and react with a second molecule of the aldehyde, resulting in a complex mixture.[3] Therefore, the synthetic application of ester-stabilized azomethine ylides (**2**) is almost exclusively limited to aromatic aldehydes or formaldehyde.[4]



1 **2**

Scheme 1.

In our efforts to develop potent antiviral agents, 4,5-disubstituted proline emerged as a useful core structure and thus an efficient synthesis was required to facilitate a thorough structure–activity relationship (SAR) study. Furthermore, the C4 and C5 substituents needed to be significantly different in reactivity to allow for independent manipulations and SAR optimization of the antiviral agents. Tsuge and co-workers reported that the [3+2] cycloaddition of *N*-substituted ester-stabilized azomethine ylides (**2**) with a dipolarophile selectively provides 2,5-*trans* proline carboxylates.[3] Various electron-deficient olefins including acrylates, nitroolefins and α,β-unsaturated sulfones have been used as the dipolarophile in this reaction. However, the use of an α,β-unsatured aldehyde as the dipolarophile has not been reported. Herein we would like to report that the reaction of *N*-substituted glycine esters (**1**) with an excess of acrolein in the presence of a catalytic amount of an acid, such as acetic acid, provides *N*-substituted 4-formyl-5-vinyl-proline carboxylates in good yield with virtually exclusive formation of 2,5-*trans* adducts (Scheme 2). To our knowledge, this is the first example reported in which glycine ester derivatives (**1**) react with two equivalents of an aldehyde to produce proline carboxylates in a one-pot process.

When *N*-benzyl glycine *t*-butyl ester (**1**, $R^1 = t$-butyl, R^2 = benzyl) was reacted with several equivalents of acrolein and a catalytic amount of acetic acid in refluxing toluene, a mixture of compounds **3** and **4** in a 2:1 ratio was obtained in a 69% combined yield (entry 1, Table 1). Apparently, compound **1** reacts with one equivalent of acrolein to form an azomethine ylide

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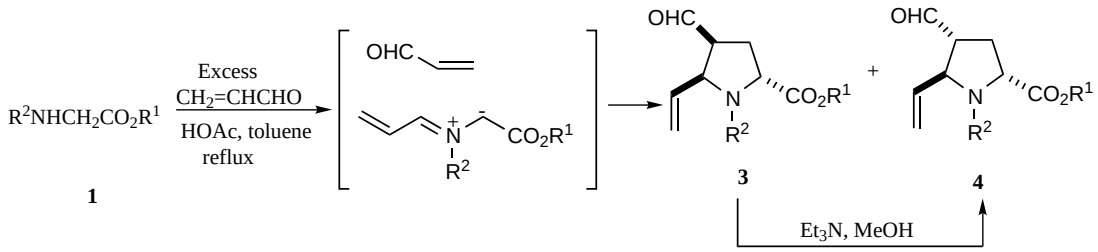

Scheme 2.

Table 1. Reaction of compounds **1** with acrolein via [3+2] cycloaddition

Entry	R^1	R^2	**3**:**4**[a,b]	**3**:**4**[a,b] (after treatment with Et_3N)	Yield (%)[c]
1	*t*-Butyl	Benzyl	2:1	1:8	69
2	*t*-Butyl	*i*-Isopropyl	2:1	1:10	72
3	Benzyl	Benzyl	3:1	1:9	41
4	Benzyl	Allyl	3:1	1:6	44
5	Methyl	*p*-Methoxybenzyl	3:1	1:7	54

[a] Ratio was determined by ^1H NMR integration.
[b] A third compound (0.5–3%) was observed.
[c] All yields are not optimized.

intermediate, which undergoes a [3+2] dipolar cycloaddition reaction with a second molecule of acrolein to produce compounds **3** and **4**. This hypothesis was supported by the fact that when a mixture of acrolein and acrylate was reacted with compound **1** under the same conditions, in addition to compounds **3** and **4**, a mixture of 4-alkoxycarbonyl-5-vinyl proline carboxylates was also formed.

The crude mixture of aldehydes **3** and **4** was reduced with $NaBH_4$ and the resulting hydroxymethyl groups were converted to acetates providing compounds **5** and **6**. Compounds **5** and **6** were separated and the stereochemical relationship among C2, C4 and C5 was determined by 2D NOE analysis (Fig. 1). Thus, compound **3** was formed as the major adduct with a *cis*-C4 to C5 relationship, consistent with Tsuge's observation that exclusive *cis*-C4–C5 adducts were obtained when **2** (R^3 = Ph) was reacted with an acrylate, presumably due to secondary orbital interaction.[5] Nevertheless, the secondary orbital interaction between the formyl and vinyl groups is probably weaker than Tsuge's case of a phenyl and ester group, resulting in lower stereoselectivity at the C4 position.

Treatment of the crude cycloaddition mixture, compounds **3** and **4** (2:1 ratio), with triethylamine in methanol overnight resulted in the thermodynamically more stable compound **4** as the major product now in an 1:8 ratio. Prolonged treatment with base does not alter the ratio any further. Variation of the R^1 and R^2 groups has little effect on either the regio- or stereoselectivity of the cycloaddition reaction. Subsequent treatment with triethylamine again provided isomer **4** as the major product with selectivity varying from 1:6 to 1:10 (entries 2–5, Table 1).

It is important to point out that the presence of a catalytic amount of acid is crucial for the success of this reaction. The yield drops significantly (as low as 5%) in the absence of acid, along with the formation of other unidentified products. This is in contrast to other [3+2] cycloaddition reactions employing ester-stabilized azomethine ylides (**2**) and acrylates where acid is not required.[3] Although acid may just facilitate the imine formation and/or [3+2] cycloaddition, it may also suppress the 1,2-addition reaction of the ylide to acrolein.[6]

It is also worth noting that the reaction of these glycine ester derivatives **1** with acrolein can be carried out in large scale. In fact, greater than 100 g of compound **4** (R^1 = *t*-butyl, R^2 = benzyl) has been prepared in a single reaction without suffering from lower yield or selectivity.

Typical experiment for the synthesis of **3** and **4** (R^1 = *t*-butyl, R^2 = benzyl): To a solution of *tert*-butyl *N*-benzyl-glycinate[7] (52 g, 235 mmol) and acetic acid (0.7 g, 11.7 mmol) in toluene (500 mL) was added acrolein (75 mL, 90% pure, 1.01 mol). The solution was refluxed for 2.5 h, followed by cooling to room temperature and

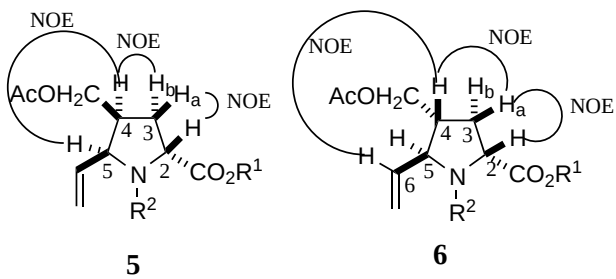

Figure 1.

solvent evaporation. The residue was dissolved in methanol (300 mL), triethylamine (5 mL, 36 mmol) was then added and the solution stirred at ambient temperature overnight. The solvents were again removed by evaporation and the residue was chromatographed eluting with 5% ethyl acetate/hexanes to afford 51 g (69%) of **3** and **4** as a 1/8 diastereomeric mixture. Spectral data of **4**: MS: m/z 316 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 9.71 (d, $J=1.2$ Hz, 1H), 7.21–7.35 (m, 5H), 5.7 (ddd, $J=17.7$, 10.2, 7.8 Hz, 1H), 5.22–5.33 (two dd, 2H), 3.94 (d, $J=13.5$ Hz, 1H), 3.93 (m, 1H), 3.61 (d, $J=13.5$ Hz, 1H), 3.49 (dd, $J=7.8$, 3.0 Hz, 1H), 2.69 (m, 1H), 2.26 (m, 1H), 1.45 (s, 9H). Anal. calcd for $C_{19}H_{25}NO_3$: C, 72.35; H, 7.99; N, 4.44. Found: C, 72.24; H, 7.73; N, 4.38. Additionally, a mixture of **3** and **4** prior to treatment with triethylamine was reduced with sodium borohydride and the hydroxyl group was converted to the corresponding acetates to provide **5** and **6**, which were then separated by column chromatography and independently identified. Spectral data of **5**: ^1H NMR (C_5D_5N): δ 7.45 (m, 5H), 5.79 (m, 1H), 5.22 (dd, $J=3.9$, 2.0 Hz, 1H), 5.19 (dd, $J=10.3$, 2.0 Hz, 1H), 4.20 (dd, $J=11.2$, 7.8 Hz, 1H), 4.07 (dd, $J=11.2$, 7.8 Hz, 1H), 4.02 (d, $J=13.7$ Hz, 1H), 3.90 (t, $J=8.8$ Hz, 1H), 3.85 (d, $J=13.7$ Hz, 1H), 3.68 (dd, $J=9.2$, 2.4 Hz, 1H), 2.95 (m, 1H), 2.17 (ddd, $J=13.2$, 8.3, 2.4 Hz, 1H), 1.97 (s, 3H), 1.93 (m, 1H), 1.46 (s, 9H); ^{13}C NMR (C_5D_5N): δ 173.5, 170.7, 140.2, 136.6, 129.2, 128.7, 127.4, 118.8, 80.6, 66.9, 65.5, 62.9, 52.9, 40.3, 32.4, 28.1, 20.8. Spectral data of **6**: MS: m/z 360 $(M+H)^+$; ^1H NMR ($CDCl_3$): δ 7.28 (m, 4H), 7.21 (m, 1H), 5.68 (m, 1H), 5.21 (m, 2H), 4.16 (dd, $J=6.3$, 10.7 Hz, 1H), 4.10 (dd, $J=7.3$, 10.7 Hz, 1H), 3.92 (d, $J=13.7$ Hz, 1H), 3.64 (d, $J=13.7$ Hz, 1H), 3.52 (m, 1H), 3.50 (m, 1H), 2.33 (m, 1H), 2.26 (m, 1H), 2.02 (s, 3H), 1.62 (m, 1H), 1.45 (s, 9H); ^{13}C NMR (C_5D_5N): δ 174.0, 171.1, 140.8, 136.2, 129.4, 128.9, 127.6, 118.4, 81.0, 69.1, 66.4, 62.6, 52.3, 43.8, 31.7, 28.4, 21.0. Anal. calcd for $C_{21}H_{29}NO_4$: C, 70.17; H, 8.13; N, 3.89. Found: C, 70.19; H, 8.07; N, 4.05.

In summary, starting from readily available glycine ester derivatives and acrolein, we have developed an efficient, regio- and stereoselective one-pot synthesis of *N*-substituted 4-formyl-5-vinyl proline carboxylates, which should be very useful intermediates for future synthetic applications. The process is suitable for large scale synthesis. An extension of this reaction utilizing substituted α,β-unsaturated aldehydes and an asymmetric version of this reaction will be a subject of future research endeavors.

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