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Et_3N-Promoted reaction of acetylenic ketones with *N*-(diphenylmethylene)-glycinates: an efficient synthesis of α,β-dehydroamino acid derivatives

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ABSTRACT

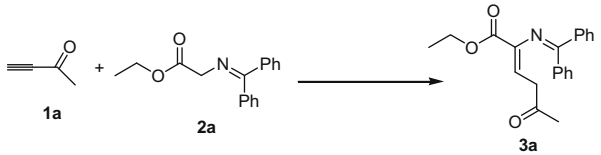
An efficient procedure for preparation of α,β-dehydroamino acids from the reaction of acetylenic ketones with *N*-(diphenylmethylene)glycinates **2** is described. The reaction of terminal acetylenic ketones with **2** promoted by Et_3N at −10 °C gave the dehydroamino acids containing ketone group in good yields.

The synthesis of α,β-dehydroamino acids has received considerable attention due to their wide utilization in organic synthesis[1] and potential pharmacological application.[2] For example, α,β-dehydroamino acids have been used to synthesize various pyridaziones,[3] non-natural amino acids.[4] Some α,β-dehydroamino acids have also been found in natural products having antimicrobial activity.[5] Many methods, such as the Mannich reactions, β-elimination, and the Wittig olefination, have been developed for the efficient synthesis of these dehydroamino acids.[6] However, these synthetic procedures are often deemed unsuitable for the preparation of dehydroamino acids containing ketone group.

Efforts have been made to develop methods for the synthesis of these functional dehydroamino acids. The reaction of electron-deficient alkynes with *N*-(bis(methylthio)methylene)glycinates in the presence of KO^{t}Bu at −78 °C gave dehydroglutamic acid derivatives in good yields.[7] Recent studies on the chemistry of organocatalysts via conjugate addition of N- and P-nucleophiles to electron-deficient alkynes have uncovered a number of interesting reactions.[8] Recently, we reported α-C-addition of 1,3-dicarbonyl compounds to acetylenic ketones catalyzed by Ph_3P.[9] We speculated that *N*-(diphenylmethylene)glycinates, which have activated methylenes,[10] would undergo a similar α-C-addition reaction to the electron-deficient alkynes. After screening various organic bases, Et_3N was found to be the proper base, and afforded the substituted dehydroamino acid derivatives in good yields. Compared to the inorganic base KO^{t}Bu, Et_3N was used as base with the obvious advantage of the ease work-up, and of the mild conditions. To the best of our knowledge, examples of preparing dehydroamino acid derivatives from acetylenic ketones using organic base have not been described. Herein, we wish to report these results.

We first chose 3-butyn-2-one (**1a**) and *N*-(diphenylmethylene)-glycinate **2a** as the standard substrates to search for suitable reaction conditions, and the results are shown in Table 1. It was observed that no product was found by TLC when PPh_3 was used as a Lewis base. Fortunately, the reaction performed in the presence of Et_3N (100 mol %) at rt for 24 h afforded a pale yellow oil in 43% yield, which was characterized as **3a**. The configuration of the carbon–carbon double bond in **3a** was determined by NOESY spectrum, and by comparison of the chemical shift value of the olefinic H with those of related compounds.[6j] 1,4-Diazabicyclo-[2,2,2]octane (DABCO) as a Lewis base gave 12% yield of product **3a**, due to low conversion of the starting materials. However, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 4-dimethylamino-pyridine (DMAP) as Lewis bases afforded only trace amount of product **3a** with small amount of unidentified mixture. As shown in Table 1, the temperature had an effect on this reaction. When the reaction temperature decreased from room temperature to

Table 1
Reactions of 3-butyn-2-one (**1a**) with **2a** under various conditions



Entry	Base (mol %)	Solvent	Temperature	Time (h)	Yield[a] (%)
1	PPh_3 (100)	CH_2Cl_2	rt	12	0
2	Et_3N (100)	CH_2Cl_2	rt	12	43
3	Et_3N (50)	CH_2Cl_2	rt	24	22
4	DABCO (100)	CH_2Cl_2	rt	12	12
5	DMAP (100)	CH_2Cl_2	rt	12	Trace
6	DBU (100)	CH_2Cl_2	rt	12	Trace
7	Et_3N (100)	CH_2Cl_2	0 °C	1	55
8	Et_3N (100)	CH_2Cl_2	−10 °C	1	57
9	Et_3N (100)	THF	−10 °C	6	16
10	Et_3N (100)	Toluene	−10 °C	6	8
11	Et_3N (100)	CH_3CN	−10 °C	1	61

[a] Isolated yields.

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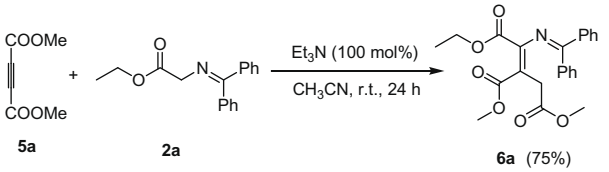
−10 °C, the yield of **3a** was increased from 43% to 57%. The yield of product was not further improved after prolonging the reaction time. Among the solvents we examined, acetonitrile was proved to be the optimum solvent, and it gave the desired product in 61% yield. The choice of THF and toluene as the solvent gave the desired product **3a** in 16% and 8% yields, respectively. Therefore, the best reaction conditions are to carry out this reaction in acetonitrile with Et_3N as Lewis base at −10 °C.

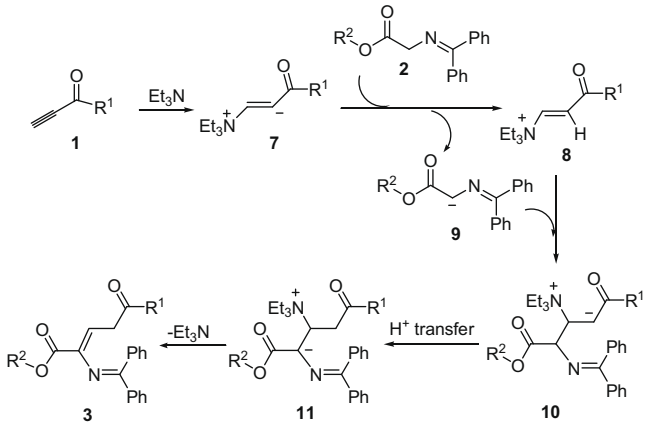
With the optimized reaction conditions in hand, a variety of terminal acetylenic ketones were subjected to the reaction,[11] and these results are summarized in Table 2. It was observed that all of the reactions proceeded smoothly under the reaction conditions, and afforded the corresponding products in good yields. The results exhibited the scope with respect to a range of aliphatic and aromatic acetylenic ketones. Aromatic acetylenic ketones showed higher reactivity than aliphatic acetylenic ketones. Treatment of 1-phenylprop-2-yn-1-one with **2a** in the presence of Et_3N (100 mol %) at −10 °C for 30 min gave the desired product **3b** in 87% yield. The substituents on the phenyl ring of aromatic acetylenic ketones had no obvious effect on the yields of the reactions. For example, the reactions of 1-(4-chlorophenyl)prop-2-yn-1-one and 1-(4-methoxyphenyl) prop-2-yn-1-one gave the corresponding products **3d** and **3g** in 81% and 83% yields, respectively. But it should be noted that no desired product was observed when a β-substituted acetylenic ketone was submitted to this reaction under our typical conditions, which might be due to the steric effect. Several derivatives of glycine esters were synthesized and tested under the reaction conditions. Methyl and isopropyl derivatives gave the corresponding products in similar yields, whereas bulky *tert*-butyl ester afforded the desired product **3k** in a lower yield. It is worthy to note that the *Z*-substituted dehydroamino acid derivative was the only product, and the *E*-isomer was not found in all cases by the spectra of ^1H and ^{13}C NMR.

When ethyl propynoate was submitted to the reaction, no desired product was found, which might be ascribed to lower reactivity of ethyl propynoate than that of acetylenic ketones. Whereas the reaction of dimethyl but-2-ynedioate (**5a**) proceeded smoothly, and afforded the corresponding product **6a** in 75% yield after stirring at room temperature for 24 h (Scheme 1).

A plausible mechanism to account for the formation of the α,β-dehydroglutamates **3** is presented in Scheme 2. Et_3N acts as a nucleophilic promoter to initiate the reaction, and produces zwitterionic intermediate **7**. The intermediate **7** deprotonates *N*-(diphenylmethylene)glycinate (**2**) to generate intermediates **8** and **9**. The intermediate **9** then undergoes conjugate addition to the intermediate **8** to give **10**, followed by proton transfer and elimination of Et_3N to give compound **3**. It is notable that enolates derived from 1,3-dicarbonyl compounds carry out through α-addition to acetylenic ketones in the presence of triphenylphosphine.[9] The deference reactivity promoted by Ph_3P might be due to its ability of stabilizing the ylide-like structure,[12] which is formed from the α-addition of the enolate to the intermediate similar to **8**. The mechanistic details of these reactions need further investigation.



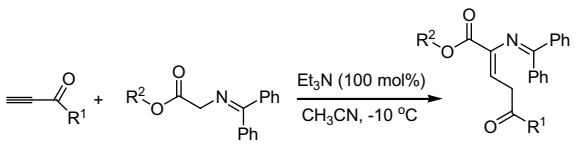
Scheme 1. The reaction of dimethyl but-2-ynedioate (**5a**) with **2a** promoted by Et_3N.



Scheme 2. Possible mechanism for the reaction of acetylenic ketones with *N*-(diphenylmethylene)glycinates.

In summary, we have described the reaction of terminal acetylenic ketones with *N*-(diphenylmethylene)glycinates promoted by Et_3N to give α,β-dehydroglutamate derivatives. Aromatic acetylenic ketones react smoothly, and afford the corresponding products in high yields. 3-Butyn-2-one as an aliphatic acetylenic ketone gives moderate yield of the desired product. This procedure for the preparation of dehydroamino acids containing ketone group will lead to building blocks and potential intermediates in organic synthesis.

Table 2
Reactions of acetylenic ketones **1** with *N*-(diphenylmethylene)glycinates **2** promoted by Et_3N



1 2 3

Entry	R^1	R^2	Time (min)	Product	Yield[a]
1	Me	Et	60	**3a**	61
2	C_6H_5	Et	30	**3b**	87
3	4-F–C_6H_4	Et	30	**3c**	90
4	4-Cl–C_6H_4	Et	20	**3d**	81
5	4-Br–C_6H_4	Et	30	**3e**	80
6	4-Me–C_6H_4	Et	30	**3f**	84
7	4-MeO–C_6H_4	Et	50	**3g**	83
8	2-Cl–C_6H_4	Et	20	**3h**	92
9	C_6H_5	Me	30	**3i**	86
10	C_6H_5	$CH(Me)_2$	40	**3j**	84
11	C_6H_5	$C(Me)_3$	50	**3k**	45

[a] Yield after purification by silica gel column chromatography.

Acknowledgments

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11. *Typical procedure*: Benzophenone Schiff base derivative of glycine ethyl ester (0.3 mmol) and Et_3N (0.3 mmol) was dissolved in 2 mL of CH_3CN. The mixture was cooled at −10 °C, and 3-butyn-2-one (0.4 mmol) was added. The resulting mixture was stirred for 1 h at −10 °C. After concentration under reduced pressure, the residue was purified by flash chromatography on silica gel using petroleum ether/ethyl acetate (10:1 to 5:1) as eluent to afford the corresponding pure product. Compound **3a**: ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm, 7.66 (d, J = 7.8 Hz, 2H), 7.41–7.28 (m, 5H), 7.13 (d, J = 7.8 Hz, 2H), 6.20 (t, J = 7.3 Hz, 1H), 3.97 (q, J = 7.2 Hz, 2H), 3.16 (d, J = 7.3 Hz, 2H), 2.06 (s, 3H), 1.09 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$), δ, ppm, 205.1, 171.3, 163.5, 142.0, 138.8, 136.9, 131.1, 129.6, 129.4, 128.3, 128.2, 128.1, 117.5, 61.0, 42.2, 30.0, 14.1; IR (KBr) ν, cm^{-1}, 1721, 1711, 1633, 1574. HRMS (EI) calcd for $C_{21}H_{21}NO_3$ [M$^+$]: 335.1521; found: 335.1519. Compound **3b**: ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm, 7.97 (d, J = 7.5 Hz, 2H), 7.62 (d, J = 7.2 Hz, 2H), 7.55–7.33 (m, 9H), 7.22 (d, J = 7.5 Hz, 2H), 6.45 (t, J = 6.9 Hz, 1H), 4.03 (q, J = 7.2 Hz, 2H), 3.81 (d, J = 6.9 Hz, 2H), 1.14 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$), δ, ppm, 196.8, 171.4, 163.4, 141.7, 138.8, 136.9, 136.5, 133.3, 131.1, 129.6, 129.3, 128.6, 128.4, 128.2, 128.1, 127.6, 118.7, 60.9, 37.7, 14.1; IR (KBr) ν, cm^{-1}, 1716, 1684, 1637, 1577. HRMS (EI) calcd for $C_{26}H_{23}NO_3$ [M]$^+$: 397.1678; found: 397.1684.
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