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N-Alkylation of diethyl acetamidomalonate: synthesis of constrained amino acid derivatives by ring-closing metathesis

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This paper is dedicated to Professor Adusumilli Srikrishna on the occasion of his 50th birthday

Abstract—An efficient method for *N*-alkylation of diethyl acetamidomalonate (DEAM) is reported. *C*-Alkenylation was achieved by treating the *N*-alkenylated DEAM with various electrophiles in the presence of Cs_2CO_3. RCM reactions of *C*- and *N*-alkenylated products gave cyclic amino acid derivatives in good yields.

1. Introduction

Aminomalonic acid **1** is a natural α-amino acid (AAA),[1] attracting increasing attention due to its inherent biological activity and as an efficient building block for unnatural amino acid derivatives. Several of its derivatives are antagonists of excitatory amino acid receptors. Compound **2** has been used to prepare unusual amino acids which are known to induce unique conformational restrictions when incorporated into biologically active peptides[2] (Fig. 1).

Diethyl acetamidomalonate (DEAM) **2** has been used in the synthesis of several AAA derivatives and in most instances, by *C*-alkylation.[3] Compound **2** has been alkylated at both reactive positions (i.e., *C*-alkylation and *N*-alkylation) by an intermolecular approach[4] to generate constrained AAA derivatives. Although DEAM **2** has been extensively used in connection with unusual AAA synthesis, its potential would be further expanded if a suitable synthetic method could be established for regioselective *C*- or *N*-alkylations in a stepwise approach.

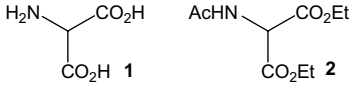

Figure 1.

As a part of our program directed towards the synthesis of constrained AAA derivatives,[5] we identified ethyl isocyanoacetate as a useful glycine equivalent suitable for dialkylation under mild reaction conditions. This methodology has delivered several constrained AAA derivatives.[6] Stepwise alkylation of this reactive glycine equivalent has not yet been realized. In this regard, classical glycine equivalents such as Schiff bases of esters of glycine are useful but, alkylation with less reactive electrophiles and bis-alkylation is still a challenging task.

In the search for glycine equivalents suitable for the synthesis of constrained AAA derivatives, we identified the commercially available and inexpensive nucleophilic glycine equivalent, DEAM **2** as an attractive option. The presence of a doubly activated position suitable for *C*-alkylation and a protected amino functionality open to *N*-alkylation is ideally suited for various heterocyclic constrained AAA derivatives, provided one could find suitable conditions for regioselective stepwise alkylation.

In this regard, a literature search indicated that many conditions are available for *C*-alkylation of **2** but no procedures are available for regioselective *N*-alkylation. Towards this goal, we screened different reaction conditions and found that Cs_2CO_3 is good for *C*-alkylation and that KH/DMF is suitable for *N*-alkylation. The results are summarized in Table 1.

It is interesting to note that even with excess KH and an alkyl halide, no *C*-alkylated product, only the *N*-alkylated product, was formed.

Keywords: Diethyl acetamidomalonate; Regioselective *N*-alkylation; Metathesis; Constrained amino acid derivatives; Heterocycles.
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Table 1. List of conditions investigated for the selective alkylation of **2**

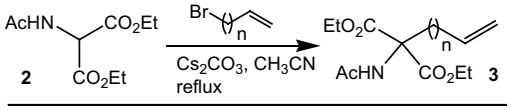
Entry	Reaction conditions	Result
1	BEMP[a], DMF, reflux	*C*-alkylation
2	BEMP[a], CH_3CN, reflux	*C*-alkylation
3	Na, EtOH, reflux	*C*-alkylation
4	NaOEt, EtOH, reflux	*C*-alkylation
5	NaH, DMF, rt	*C*-alkylation
6	NaH, DMF, reflux	*C*-alkylation
7	KH, DMF, reflux	*N*-alkylation
8	CuI, DMF, *N*,*N*′-dimethylethylenediamine, reflux	*C*- and *N*-alkylation

[a] BEMP = 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine.

For *C*-alkenylation, Cs_2CO_3 is advantageous in view of its easy handling and simpler work-up as compared to other reaction conditions. *C*-Alkenylated derivatives were synthesized by alkenylation of **2** using Cs_2CO_3 as base (Scheme 1).

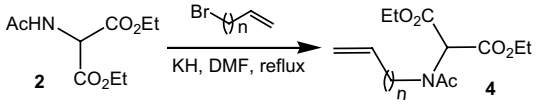
The proton NMR spectra of **3a**–**d** exhibited the characteristic signals indicating the presence of the terminal olefin moiety. The absence of an α-*C* proton and presence of an amide proton ($\delta \approx 6.8$) confirmed the structure of these *C*-alkenylated products.

After considerable experimentation we found that KH–DMF was suitable for *N*-alkenylation. When DEAM and an unsaturated alkyl bromide were refluxed in the presence of KH in DMF, *N*-alkenylation products were obtained in good yields (Scheme 2). These compounds were characterized by ^1H and ^{13}C NMR spectral data. The presence of characteristic signals for a terminal olefin moiety, an α-CH ($\delta \approx 5.8$) and the absence of NH in the ^1H NMR spectra confirmed the structure of the products. In addition, the IR spectra of **4** confirmed *N*-alkenylation due to the disappearance of the NH stretching band.



n	Compound	% Yield
1	**3a**	99
2	**3b**	48
3	**3c**	47
4	**3d**	46

Scheme 1. *C*-Alkenylation of DEAM.



n	Compound	% Yield
1	**4a**	53
3	**4b**	49
4	**4c**	48

Scheme 2. *N*-Alkenylation of DEAM.

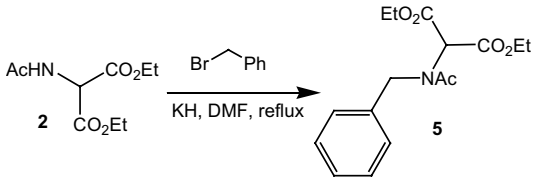
Attempts with 4-bromo-1-butene under similar reaction conditions were unsuccessful. The reason may be due to polymerization of 4-bromo-1-butene or competitive elimination of 4-bromo-1-butene to give 1,3-butadiene. When the reaction was performed with benzyl bromide, product **5** was obtained in 35% yield (Scheme 3). We did not observe any *O*-alkylation, only *N*-alkylated products were obtained with KH/DMF conditions.

C-Alkenylation of compounds **4** using Cs_2CO_3 as base gave dialkenylated products in good yields which were characterized by ^1H and ^{13}C NMR spectroscopic data and HRMS (Scheme 4).

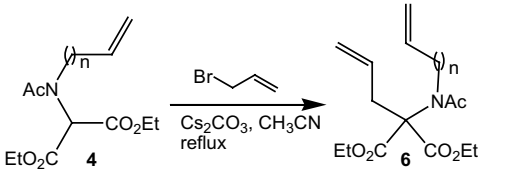
Attempts to extend this *C*-alkenylation to other unsaturated electrophiles, such as 4-bromo-1-butene, 5-bromo-1-pentene, 6-bromo-1-hexene, were unsuccessful. Following *N*-alkenylation α-position is hindered and therefore, S_N2 type alkylation is not facile. It seems that a reactive electrophile such as allyl bromide is effective for *C*-alkylation of *N*-alkenylated products.

Having prepared the required dialkenylated compounds **6**, they were then subjected to ruthenium-catalyzed RCM reactions[7] to obtain the corresponding cyclic amino acid derivatives. The RCM reaction was carried out in dry DCM at room temperature and under high dilution. Use of Grubbs' 1st generation catalyst **7** for RCM of **6** gave a mixture of products as indicated by TLC analysis (Fig. 2).

As expected, use of the 2nd generation catalyst **8**, gave RCM products in good yields. ^1H NMR spectral data for the products **9** showed the presence of two different multiplets which correspond to the two non-equivalent olefinic protons. All these products exhibited characteristic carbonyl absorption bands at 1741 cm^{-1} and 1649 cm^{-1} for the ester and amide carbonyls as well as C=C stretches. (Scheme 5).



Scheme 3.



n	Compound	% Yield
1	**6a**	61
3	**6b**	91
4	**6c**	92

Scheme 4. Dialkenylated derivatives of DEAM.

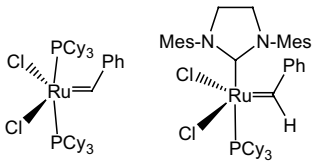
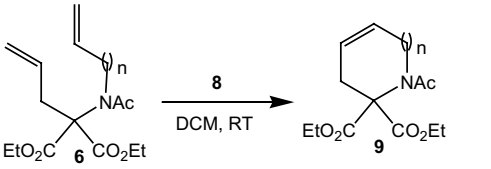


Figure 2. Grubbs' catalysts used for RCM reactions.



n	Compound	% Yield
1	**9a**	83
3	**9b**	91
4	**9c**	92

Scheme 5. RCM of dialkenylated products **6**.

In conclusion, we have developed a simple method for *N*-alkenylation of **2** and synthesized six-, eight- and nine-membered nitrogen-containing heterocycles incorporating an aminomalonic acid derivative via a RCM reaction as the key step.

2. Experimental

2.1. General procedure for *C*-alkenylation

To a solution of DEAM **2** (or *N*-alkenylated DEAM) in acetonitrile, cesium carbonate and alkenyl bromide were added and reaction mixture refluxed with stirring for 12–16 h. Then, the reaction mixture was cooled to room temperature and filtered, washed with water, brine and dried (Na_2SO_4). Purification by chromatography (SiO_2; petroleum ether–EtOAc, 4:1) gave the required compound as a thick liquid.

2.2. General procedure for *N*-alkenylation

To a solution of KH in dry DMF, DEAM **2** and alkenyl bromide were added and the mixture refluxed for 10–16 h. The reaction mixture was cooled to room temperature and quenched with ethyl acetate. Usual workup followed by extraction with ethyl acetate (3×25 mL) gave the alkenylated product. Purification of the crude product by column chromatography (SiO_2; petroleum ether–ethyl acetate, 8.5:1.5) gave a dense liquid.

2.3. General procedure for RCM

A solution of dialkenylated DEAM **6** in dry, degassed DCM and Grubbs' 2nd generation catalyst **8** was stirred at room temperature for 3–10 h (until completion of the reaction, TLC monitoring). Then, the reaction mixture was concentrated in vacuo. Purification of the crude product by column chromatography (SiO_2; petroleum ether–ethyl acetate, 4:1) afforded the product as a thick liquid.

2.4. Diethyl 2-acetamido-2-allylmalonate 3a[8]

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 (6H, t, $J = 6.95$ Hz), 2.04 (3H, s), 3.01 (2H, d, $J = 7.6$ Hz), 4.25 (4H, q, $J = 6.96$ Hz), 5.09–5.13 (2H, m), 5.57–5.59 (1H, m), 6.8 (1H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 13.8, 22.8, 36.8, 64.4, 66.0, 119.7, 131.7, 167.5, 168.9.

2.5. Diethyl 2-acetamido-2-(but-3-enyl)malonate 3b[9]

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 (6H, t, $J = 7.1$ Hz), 1.88–1.94 (2H, m) 2.04 (3H, s), 2.42–2.48 (2H, m), 4.25 (4H, q, $J = 7.1$ Hz), 4.94–5.04 (2H, m), 5.69–5.79 (1H, m), 6.8 (1H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 14.0, 23.1, 28.1, 31.4, 62.7, 66.4, 115.5, 137.1, 168.2, 169.1.

2.6. Diethyl 2-acetamido-2-(pent-4-enyl)malonate 3c[10]

^{1}H NMR (400 MHz, $CDCl_3$): 1.20–1.22 (2H, m), 1.26 (6H, t, $J = 7.1$ Hz), 1.98–2.08 (2H, m), 2.1 (3H, s), 2.30–2.38 (2H, m), 4.25 (4H, q, $J = 7.1$ Hz), 4.93–5.02 (2H, m), 5.72–5.80 (1H, m), 6.8 (1H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 14.0, 23.1, 31.7, 33.2, 62.5, 66.5, 115.0, 137.9, 168.1, 169.0.

2.7. Diethyl 2-acetamido-2-(hex-5-enyl)malonate 3d

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.06–1.18 (2H, m), 1.26 (6H, t, $J = 7.1$ Hz), 1.30–1.46 (2H, m), 1.96–2.02 (2H, m), 2.03 (3H, s), 2.29–2.35 (2H, m), 4.25 (4H, q, $J = 7.1$ Hz), 4.90–5.01 (2H, m), 5.70–5.81 (1H, m), 6.80 (1H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 14.0, 22.9, 23.1, 28.4, 31.9, 33.4, 62.5, 66.6, 114.6, 138.4, 168.3, 168.9.

2.8. Diethyl 2-(*N*-allylacetamido)malonate 4a

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28 (6H, t, $J = 7.6$ Hz), 2.17 (3H, s,), 4.08 (2H, t, $J = 2.4$ Hz), 4.23 (4H, q, $J = 7.5$ Hz), 5.14–5.32 (2H, m), 5.64 (1H, s), 5.78–5.88 (1H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 14.1, 21.5, 50.5, 60.4, 62.1, 116.8, 133.3, 166.2, 171.6.

2.9. Diethyl 2-(*N*-(pent-4-enyl)acetamido)malonate 4b

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (6H, t, $J = 7.1$ Hz), 1.65–1.73 (2H, m), 2.04–2.11 (2H, m), 2.18 (3H, s), 3.39 (2H, t, $J = 7.9$ Hz), 4.25–4.29 (4H, m), 5.01–5.07 (2H, m), 5.26 (1H, s), 5.72–5.82 (1H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 14.0, 21.2, 28.3, 30.8, 48.3, 61.4, 62.1, 115.8, 137.1, 166.4, 171.3.

2.10. Diethyl 2-(*N*-(hex-5-enyl)acetamido)malonate 4c

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.27 (6H, t, $J = 7.0$ Hz), 1.35–1.44 (2H, m), 1.51–1.64 (2H, m), 2.03–2.10 (2H, m), 2.18 (3H, s), 3.85 (2H, t, $J = 8.2$ Hz), 4.20–4.36 (4H, m), 4.95–5.03 (2H, m), 5.28 (1H, s), 5.72–5.82

(1H, m). ^{13}C NMR (75.43 MHz, $CDCl_3$): δ 14.1, 21.2, 26.1, 28.8, 33.3, 48.8, 61.3, 62.1, 115.1, 137.9, 166.3, 171.1.

2.11. Diethyl 2-(*N*-benzylacetamido)malonate 5

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.19 (6H, t, J = 7.3 Hz), 2.15 (3H, s), 4.01–4.09 (2H, m), 4.11–4.17 (2H, m), 4.70 (2H, s), 5.50 (1H, s), 7.24–7.39 (5H, m). ^{13}C NMR (75.43 MHz, $CDCl_3$): δ 14.1, 21.7, 51.5, 60.9, 62.1, 126.2, 127.5, 128.6, 136.3, 166.2, 172.1.

2.12. Diethyl 2-allyl-2-(*N*-allylacetamido)malonate 6a

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 (6H, t, J = 7.1 Hz), 2.11 (3H, s), 2.90 (2H, d, J = 6.1 Hz), 3.91 (2H, d, J = 4.3 Hz), 4.20 (4H, q, J = 7.0 Hz), 5.07–5.18 (2H, m), 5.22–5.44 (2H, m), 5.87–5.95 (2H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 13.9, 22.2, 38.3, 49.6, 61.8, 71.7, 116.8, 119.2, 132.7, 134.4, 167.7, 172.5. HRMS m/z: $(M + Na)^+$ found 320.1489; calcd 320.1474.

2.13. Diethyl 2-allyl-2-(*N*-(pent-4-enyl)acetamido)malonate 6b

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.27 (6H, t, J = 7.2 Hz), 1.71–1.79 (2H, m), 1.92–2.07 (2H, m). 2.14 (3H, s), 2.93 (2H, d, J = 6.95 Hz), 3.33 (2H, t, J = 5.1 Hz), 4.10 (4H, q, J = 7.2 Hz), 5.01–5.06 (2H, m), 5.08–5.15 (2H, m), 5.71–5.82 (1H, m), 5.90–6.01 (1H, m). ^{13}C NMR (75.43 MHz, $CDCl_3$): δ 13.9, 22.1, 28.9, 30.9, 38.6, 46.8, 61.8, 71.4, 115.8, 119.1, 132.7, 136.99, 168.0, 171.7. HRMS m/z: $(M + Na)^+$ found 348.1785; calcd 348.1787.

2.14. Diethyl 2-allyl-2-(*N*-(hex-5-enyl)acetamido)malonate 6c

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.27 (6H, t, J = 7.2 Hz), 1.31–1.41 (2H, m), 1.62–1.67 (2H, m), 2.04–2.13 (2H, m), 2.14 (3H, s), 2.93 (2H, d, J = 6.95 Hz), 3.25 (2H, t, J = 6.2 Hz), 4.10 (4H, q, J = 7.2 Hz), 4.95–5.05 (2H, m), 5.12–5.15 (2H, m), 5.71–5.80 (1H, m), 5.90–6.01 (1H, m). ^{13}C NMR (75.43 MHz, $CDCl_3$): δ 14.1, 21.5, 26.1, 28.7, 33.2, 33.5, 49.2, 61.1, 61.8, 115.0, 117.7, 134.5, 138.0, 168.9, 170.7. HRMS m/z: $(M + Na)^+$ found 362.1926; calcd 362.1943.

2.15. Diethyl 1-acetyl-1,6-dihydropyridine-2,2-(3*H*)-dicarboxylate 9a

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (6H, t, J = 7.1 Hz), 2.10 (3H, s), 2.86–2.89 (2H, m), 4.03–4.05 (2H, m), 4.30 (4H, q, J = 7.0 Hz), 5.68–5.72 (1H, m), 5.84–5.90 (1H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 14.1, 22.4, 32.3, 45.6, 62.2, 66.7, 123.0, 123.1, 168.3, 172.7.

2.16. Diethyl 1-acetyl-7,8-dihydroazocine-2,2-(1*H*,3*H*,6*H*)-dicarboxylate 9b

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.30 (6H, t, J = 7.1 Hz), 1.72–1.78 (2H, m), 2.10 (2H, m), 2.20 (3H, s), 2.80 (2H, d, J = 7.3 Hz), 3.43 (2H, t, J = 5.5 Hz), 4.20 (4H, q, J = 7.1 Hz), 5.80–5.84 (2H, m). ^{13}C NMR (75.43 MHz, $CDCl_3$): δ 14.0, 21.9, 24.2, 29.3, 31.5, 47.0, 62.0, 73.8, 127.1, 132.5, 167.7, 172.5. HRMS m/z: $(M + 1)^+$ found 298.1643; calcd 298.1654.

2.17. Diethyl 1-acetyl-6,7,8,9-tetrahydro-1*H*-azonine-2,2-(3*H*)-dicarboxylate 9c

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21 (6H, t, J = 7.1 Hz), 1.46–1.54 (2H, m), 1.85–1.94 (2H, m), 2.14 (3H, s), 2.20–2.32 (2H, m), 2.90 (2H, d, J = 7.3 Hz), 3.40–3.50 (2H, m), 4.20 (4H, q, J = 7.1 Hz), 5.60–5.68 (2H, m). ^{13}C NMR (75.43 MHz, $CDCl_3$): δ 14.1, 22.3, 22.8, 24.4, 28.1, 32.2, 41.9, 61.9, 72.4, 126.0, 132.1, 168.0, 172.7. HRMS m/z: $(M + 1)^+$ found 312.1817; calcd 312.1811.

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