Imidoylation Reactions: A Simple Direct Synthesis of 3-Amino-2-alkenoic Esters (β-Enaminoesters)

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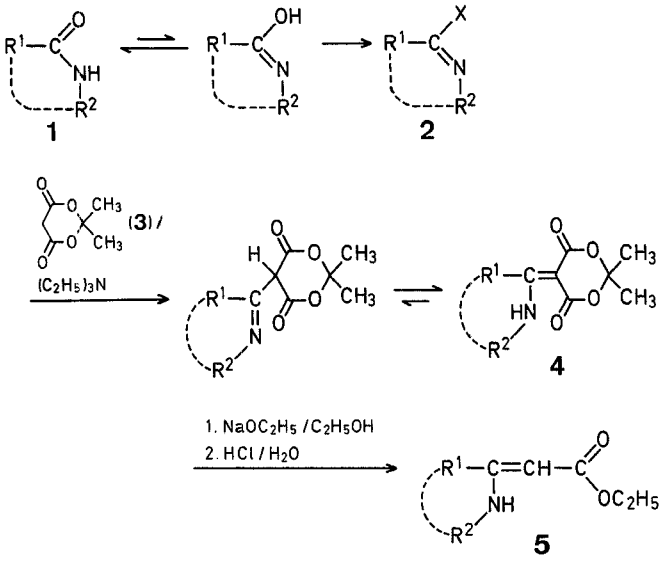
The α-acylation of alkanoic or malonic esters by carboxylic acids or, more generally, reactive acid derivatives constitutes the principal method for the synthesis of 3-oxoalkanoic esters[1-4]. The acylation of isopropylidene malonate (Meldrum acid, **2**) with acid chlorides followed by a monodecarboxylating transesterification reaction is one of the most efficient methods[5] of this type. On the other hand, only few methods for the synthesis of the enamines of 3-oxoalkanoic esters, i.e., 3-amino-2-alkenoic esters (β-enamino esters, **5, 9**), have hitherto been described[6] although these compounds are important intermediates for heterocyclic and natural products synthesis.

A general synthesis of 3-amino-2-alkenoic esters of the type **5** might be based on the imidoylation of a suitable malonic ester such as isopropylidene malonate (**3**, Meldrum acid) with reactive carboxylic acid *N*-derivatives such as alkyl carboximidates (**2**, X = *O*-alkyl), alkyl carboximidothioates (**2**, X = *S*-alkyl), and carboximidic chlorides (**2**, X = Cl).

Activated carboxylic acid *N*-derivatives such as *O*-alkyllactims[7,8], alkyl carboximidates[9,10], alkyl carboximidothioates[11], and *S*-alkylthiolactims[12] react in a similar manner with numerous carbanions. The particular choice of Meldrum acid **(3)** for these reactions is based on the high reactivity of **3** and on the ease of monodecarboxylating transesterification of the (1-aminoalkylidene)-malonic esters **4** in basic[8,9], acid, or neutral[13] medium.



As regards the use of lactim derivatives (cyclic **2**) in the above sequence, the yield of imidoylation products **4** depends strongly on the ring size of **2** (derived from an *N*-unsubstituted lactam **1**) and on the choice of the function X. Thus, for example, the *O*-alkyllactims **2**, $R^1—R^2 = —(CH_2)_{11}—$, X = *O*-alkyl, and the corresponding *S*-alkylthiolactims **2**, $R^1—R^2 = —(CH_2)_{11}—$, X = *S*-alkyl, derived from 12-dodecanelactam [**1**, $R^1—R^2 = —(CH_2)_{11}—$] on attempted reaction with **3** give the expected product **4** in 0 or 6% yield, respectively, whereas with *O*-alkyllactims derived from 5-, 6-, or 7-membered lactams [**1**, $R^1—R^2 = —(CH_2)_{3-5}—$] better yields of **4** are obtained. The cyclic carboximidic chlorides **2** (X = Cl) react better with Meldrum acid **(3)**; thus, in the case $R^1—R^2 = —(CH_2)_{11}—$ an 81% yield of **4** is obtained.

We have carried out a sequence analogous to the above one [of which one example with $R^1—R^2 = —(CH_2)_{11}—$ is given here] using *N*-methyllactim derivatives (**7**, derived from *N*-methyllactams) in place of the carboximidic acid derivatives **2**. Being tertiary amides, *N*-methyllactams **(6)** are less reactive than primary and secondary amides **(1)**. The same applies to the corresponding lactim derivatives which may be regarded as activated derivatives of the lactams. Thus, conversion of *N*-methyl-4-butanelactam (**6**, n = 3) into the cyclic 1-ethoxy-*N*-methylalkeniminium salt **7** ($X^1 = OC_2H_5$, n = 3)[14] which represents an *N*-methyl analog of the activated secondary amide

derivatives **2** is a still insufficient activation for the reaction with Meldrum acid **(3)**. In this case, the corresponding cyclic *N*-methyl-2-methylthioalkaniminium salt **7** ($X^1 = SCH_3$, n = 3) may be used for the preparation of the alkylidenemalonic diester **8**. In contrast to this, the higher cyclic *N*-methyl-2-methylthioalkaniminium salts **7** ($X^1 = SCH_3$, n = 4, 5) derived from 5-pentanelactam or 6-hexanelactam (ε-caprolactam) do not react with the active methylene compound **3**. Sufficient activation for the reaction with Meldrum acid **(3)** may be achieved, however, by converting the *N*-methyllactams **6** into the cyclic 1-chloro-*N*-methylalkaniminium chlorides **7** ($X^1 = X^2 = Cl$) by treatment with phosgene. Such 1-chloroalkaniminium chlorides react readily with several active methylene compounds[15].

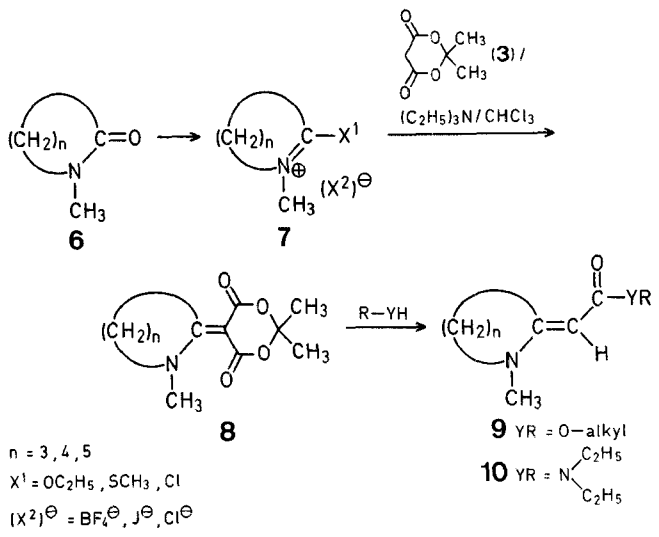


Table 1. Isopropylidene (1-Methylazacycloalkan-2-ylidene)-malonates **(8)**

8	n	X^1 in 7	X^2 in 7	Yield [%]	m.p. [°C] (solvent)	Molecular formula[a]
a	3	OC_2H_5	BF_4	0	151–152° (ethanol)	$C_{11}H_{15}NO_4$ (225.2)
		SCH_3	J	76		
		Cl	Cl	97		
b	4	SCH_3	J	0	157–159° (ethanol)	$C_{12}H_{17}NO_4$ (239.3)
		Cl	Cl	55		
c	5	SCH_3	J	0	131° (methanol)	$C_{13}H_{19}NO_4$ (241.3)
		Cl	Cl	66		
d	11	Cl	Cl	36	183–184° (methanol)	$C_{19}H_{31}NO_4$ (337.45)

[a] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.32; H, ±0.13; N, ±0.24.

The condensation products **8** may be converted into the 2-alkenoic esters **9** or the 2-alkenamides **10** by monodecarboxylating transesterification in basic (Method A) or neutral medium (Method B) or by heating with secondary amines, respectively.

2-Ethoxyazacyclotridec-1-ene [2, R^1—R^2 = —$(CH_2)_{11}$—, X = O—C_2H_5]:
Prepared from 12-dodecanelactam [**1**, R^1—R^2 = —$(CH_2)_{11}$—] according to Ref.[16]; yield: 57%; b.p. 108 °C/0.7 torr.

$C_{14}H_{27}NO$	calc.	C 74.61	H 12.08	N 6.22
(225.4)	found	74.98	12.06	6.30

I.R. (neat): ν = 2920, 1440, 1250 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): δ = 1.1–1.9 (m, 21 H); 2.27 (t, J = 6 Hz, 2 H); 3.28 (t, J = 7 Hz, 2 H); 4.04 ppm (q, J = 7 Hz, 2 H).

2-Methylthioazacyclotridec-1-ene Hydroiodide [2, R^1—R^2 = —$(CH_2)_{11}$—, X = S—CH_3]:
Prepared from 12-dodecanelactam [**1**, R^1—R^2 = —$(CH_2)_{11}$—] by treatment with phosphorus(V) sulfide in benzene (cf. Ref.[17]) followed by alkylation of the resultant thiolactam with methyl iodide in dichloromethane; yield: 64%; m.p. 122 °C.

$C_{13}H_{26}JNS$	calc.	C 43.94	H 7.32	N 3.94	J 35.77
(355.5)	found	44.30	7.14	4.02	35.34

I.R. ($CHBr_3$): ν = 3075, 1595 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): δ = 1.1–2.1 (m, 18 H); 2.90 (s, 3 H); 3.2–3.95 (m, 4 H); 11.00 ppm (s, 1 H).

***N*-Methyl-12-dodecanelactam (6, n = 11):**
Prepared from 12-dodecanelactam according to Ref.[18]; yield: 20%; b.p. 140 °C/0.05 torr.

$C_{13}H_{25}NO$	calc.	C 73.88	H 11.92	N 6.63
(211.34)	found	73.64	11.98	6.52

I.R. (neat): ν = 2960, 2920, 1635 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): δ = 1.1–2.0 (m, 21 H); 2.1–2.5 (m, 2 H); 2.96 (d, 3 H, J = 6 Hz); 3.1–3.4 ppm (m, 2 H).

Reaction of 2-Methylthioazacyclotridec-1-ene Hydroiodide [2·HJ, $R^1 = R^2$ = —$(CH_2)_{11}$—, X = SCH_3] and of 1-Methyl-2-methylthioazoniacycloalk-1-ene Iodides (7, $X^1 = SCH_3$, X^2 = J, n = 3, 4, 5) with Meldrum Acid (3); General Procedure:
A mixture of the salt **2** or **7**[16] (1.0 equiv), Meldrum acid[17] (**3**; 1.0 equiv), and triethylamine (0.1 equiv for **7**, 1.1 equiv for **2**) in benzene (400 ml for 1 mol of **2** or **7**) is refluxed overnight. The benzene is then evaporated and the residual product (**4** or **8**) recrystallized.

Table 2. 3-Amino-2-alkenoic Esters **(9)** and *N,N*-Diethyl-(1-methylpyrrolidin-2-ylidene)-acetamide **(10)**

Product	n	—YR	Method	Yield [%]	b.p. [°C]/torr	Molecular formula[a] or Lit. Data
9a	3	—OC_2H_5	A	90	93–95°/0.01	isolated by T.L.C.[19]
			B	95		
9b	3	—O—C_3H_7-*i*	B	80	98–100°/0.05	$C_{10}H_{17}NO_2$ (183.2)
9c	3	—O—CH_2—C_6H_5	B	65	166–168°/0.02	$C_{14}H_{17}NO_2$ (231.3)
9d	3	—O—C_4H_9-*t*	B	43	93–95°/0.03	$C_{11}H_{19}NO_2$ (197.3)
9e	4	—OC_2H_5	A	56	111–112°/0.5	$C_{10}H_{17}NO_2$ (183.2)
			B	95		
9f	5	—OC_2H_5	A	72	106–108°/0.05	$C_{11}H_{19}NO_2$ (197.3)
			B	95		
9g	11	—OC_2H_5	B	40	[b]	
10	3	—$N(C_2H_5)_2$	B	56	116–118°/0.05	$C_{11}H_{20}N_2O$ (196.3)

[a] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.28; H, ±0.32; N, ±0.33; exception: **10**, C, ±0.44.
[b] T.L.C. (Kieselgel 60F 254, Merck), eluting with ethyl acetate/cyclohexane (7/3), R_F = 0.66.

Reaction of 2-Chloro-1-methylazoniacycloalk-1-ene Chlorides (7, $X^1=X^2=Cl$) with Meldrum Acid (3); General Procedure for the Preparation of Isopropylidene (1-Methylazacycloalkan-2-ylidene)-malonates (8) from *N*-Methyllactams (6):

A 20% solution of phosgene in toluene (500 ml per mol of **6**) is added dropwise to a stirred solution of the *N*-methyllactam (**6**; 1.0 equiv) in chloroform (400 ml per 1 mol of **6**) at 0 °C, and stirring is continued for 5 h at 0 °C. Then, Meldrum acid (**3**; 1.0 equiv) is added, followed by the slow addition of a solution of triethylamine (280 ml per mol of **6**) in chloroform (300 ml per mol of triethylamine). The mixture is stirred at room temperature overnight. The organic layer is separated, washed with water (3 × 50 ml), dried with sodium sulfate, and concentrated in vacuo. The solid residue is triturated with ether or ethyl acetate and recrystallized from an appropriate solvent.

Cleavage of Compounds 4 and 8 to the 3-Amino-2-alkenoic Esters 5 or 9 or to the 3-Amino-2-alkenamides 10; General Procedures:

Method A: The cyclic ester **4** or **8** (1.0 equiv) is added to a solution of sodium ethoxide (1.0 equiv) in ethanol (2000 ml per mol) and the mixture is refluxed overnight. The solvent is then evaporated in vacuo. Water (1500 ml per mol) and 10% hydrochloric acid are added, the latter until pH 6 is reached. The resultant mixture is extracted with chloroform (3 × 500 ml per mol of reactants), dried with sodium sulfate, and evaporated. The residual crude product is recrystallized from an appropriate solvent.

Method B: A mixture of the cyclic ester **4** or **8** (0.02 mol) and the respective alcohol or amine (50 ml) is heated for 30 min at a temperature 25 °C above the point at which decomposition with evolution of carbon dioxide sets in [with higher boiling reagents such as *t*-butanol (0.12 mol), benzyl alcohol (0.06 mol), and ethanethiol (25 ml), a solution of the reagent in acetone is used]. The resultant mixture is evaporated with a rotavapor. The crude product is distilled under reduced pressure.

Ethyl Azacyclotridecan-2-ylideneacetate [5, R^1—R^2 = —$(CH_2)_{11}$—]:

Prepared by Method B; yield: 95%; b.p. 167–169 °C/0.05 torr; m.p. 56 °C.

$C_{16}H_{29}NO_2$	calc.	C 71.86	H 11.97	N 5.24
(267.4)	found	71.74	10.99	5.42

I.R. (neat): ν = 3360, 1635, 1600 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): δ = 1.25 (t, J = 7 Hz, 3H); 1.25–1.9 (m, 18H); 2.0–2.4 (m, 2H); 3.0–3.5 (m, 2H); 4.12 (q, J = 7 Hz, 2H); 4.44 (s, 1H); 8.3 ppm (broad s, 1H).

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Table 3. Spectrometric Data of Compounds **8**

8	I.R. ($HCBr_3$) $\nu_{C=O}$ [cm^{-1}]	$\nu_{C=N}$	^{1}H-N.M.R. ($CDCl_3/TMS_{int}$, 60 MHz) δ [ppm]
a	1695, 1650	1560	1.68 (s, 6H); 1.9–2.4 (m, 2H); 3.18 (s, 3H); 3.25–3.6 (m, 2H); 3.6–3.95 (m, 2H)
b	1690, 1640	1580	1.68 (s, 6H); 1.7–2.0 (m, 4H); 3.30 (s, 3H); 3.2–3.3 (m, 4H)
c	1700, 1650	1580	1.82 (s, 6H); 1.7–2.0 (m, 6H); 3.1–3.4 (m, 2H); 3.38 (s, 3H); 3.6–3.9 (m, 2H)
d	1705, 1640	1585	1.1–1.2 (m, 18H); 1.65 (s, 6H); 2.8–3.5 (m, 4H); 3.20 (s, 3H)

Table 4. Spectrometric Data of Compounds **9** and **10**

Compound	I.R. (neat) $\nu_{C=O}$ [cm^{-1}]	$\nu_{C=N}$	^{1}H-N.M.R. ($CDCl_3/TMS_{int}$, 60 MHz) δ [ppm]
9a	1670	1590	1.24 (t, J = 7, 3H); 1.7–2.2 (m, 2H); 2.82 (s, 3H); 2.9–3.5 (m, 4H); 4.09 (q, J = 7, 2H); 4.46 (s, 1H)
9b	1670	1590	1.22 (d, J = 6, 6H); 1.7–2.3 (m, 2H); 2.80 (s, 3H); 2.9–3.6 (m, 4H); 4.45 (s, 1H); 5.00 (q, J = 6, 1H)
9c	1675	1595	1.55–2.15 (m, 2H); 4.35 (s, 3H); 2.9–3.4 (m, 4H); 4.50 (s, 1H); 5.08 (s, 2H); 7.1–7.4 (m, 5H)
9d	1675	1595	1.43 (s, 9H); 1.8–2.2 (m, 2H); 2.75 (s, 3H); 2.9–3.5 (m, 4H); 3.55 (s, 1H)
9e	1680	1570	1.22 (t, J = 7, 3H); 1.4–2.0 (m, 2H); 2.80 (s, 3H); 2.9–3.4 (m, 4H); 4.06 (q, J = 7, 2H); 4.52 (s, 1H)
9f	1670	1575	1.28 (t, J = 7, 3H); 1.5–2.0 (m, 6H); 3.02 (s, 3H); 3.2–3.7 (m, 4H); 4.22 (q, J = 7, 2H); 4.58 (s, 1H)
9g	—		1.22 (t, J = 7, 3H); 1.55–1.85 (m, 18H); 2.3–2.6 (m, 2H); 3.82 (s, 3H); 2.7–3.1 (m, 2H); 4.10 (q, J = 7, 2H); 4.52 (s, 1H)
10	1625	1570	1.13 (t, J = 7, 6H); 1.7–2.2 (m, 2H); 2.80 (s, 3H); 3.0–3.65 (m, 8H); 4.66 (s, 1H)

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