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Reactivity of 2-acylaminoacrylates with ketene diethyl acetal; [2 + 2] cycloadditions *vs.* tandem condensations†

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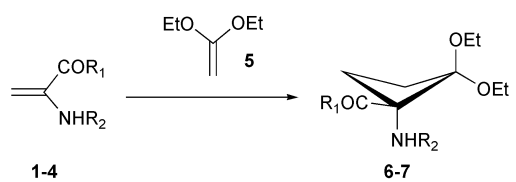
The reactivity of 2-acylaminoacrylates with ketene diethyl acetal can be modulated by means of thermal conditions to yield cyclobutanes for the preparation of protected β-hydroxycyclobutane-α-amino acids, or catalytic conditions that yield cyclohexanes by tandem condensations to obtain interesting building blocks that are alternatives to Danishefsky's diene.

Due to the main role that 2-acylaminoacrylates have played in the field of novel amino acids,[1] these compounds have been the subject of several synthetic studies[2] involving reactions such as cyclopropanations,[3] Diels–Alder reactions,[4] hydrogenations,[5] and nucleophilic additions.[6] However, these compounds have never been investigated in terms of [2 + 2] reactions, while in this field methyl acrylate, an olefin acceptor, has been widely used as a starting material in [2 + 2] cycloadditions.[7] In the context of our research programme on the synthesis of conformationally restricted hydroxy amino acids[8] and in order to obtain 1-aminocyclobutane-1-carboxylic acids with oxygen groups at C-2, which are significant targets in bioorganic chemistry,[9] we studied the cycloaddition of 2-acylaminoacrylates **1–4** with ketene diethyl acetal **5**. The reaction gave cyclobutane-α-amino acid derivatives **6–7** and these could be easily transformed into β-hydroxycyclobutane-α-amino acids (c_4Ser), which are analogues of serine. Since c_5Ser and c_6Ser have been described and c_6Ser even incorporated into peptides,[10] the kind of restricted amino acid described here is a very important target in peptide chemistry due to the lack of available c_4Ser (Scheme 1).

Taking into account the mechanism proposed for the thermal [2 + 2] cycloaddition between acrylates and ketene diethyl acetal, we attempted the reaction in two polar solvents (acetonitrile and *tert*-butanol).[11] In the case of substrates **1** or **2** the reaction did not proceed at all. Fortunately, the reactions with methyl 2-benzamido- and 2-acetamidoacrylates (**3** and **4**) gave the desired cyclobutane core in yields similar to those obtained with acrylates[7] (Table 1). The structure of compound **7** was unambiguously determined by X-ray diffraction‡ (Figure 1).

In order to assess catalytic conditions, we carried out the reaction at low temperature in the presence of aluminium catalysts. When $AlMe_3$ was employed only traces of **7** were detected because of the propensity of this compound to undergo the ring-opening reaction. To prevent this, we used the soft and bulky Lewis acid methylaluminium bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD)[12] (Table 1).



Scheme 1 Reaction of 2-acylaminoacrylates and ketene diethyl acetal.

Unexpectedly, the cyclobutane core was not obtained and the reaction led to a cyclohexane ring by a sequential Michael-aldol-type process. To the best of our knowledge, this reactivity of ketene diethyl acetal has been explored only in quinone chemistry and has recently been used in the synthesis of optically active lactones.[13] The yield was increased by the use of methylaluminium bis(2,6-di-*tert*-butyl-4-bromophenoxide) (MABR) as catalyst (Table 1, Scheme 2).

Table 1 Reactivity of 2-acylaminoacrylates with ketene diethyl acetal

Substrate	R_1	R_2	Method[a]	Catalyst	Product	Yield[b]
1	OH	Ac	A	–	–	–
2	NH^{i}Pr	Ac	A	–	–	–
3	OMe	Bz	A	–	**6**	51%
4	OMe	Ac	A	–	**7**	64%[c]
4	OMe	Ac	B	$AlMe_3$	**7**	traces
4	OMe	Ac	B	MAD	**10**	51%
4	OMe	Ac	B	MABR	**10**	80%

[a] Method A corresponds to thermal conditions in *tert*-butanol at 83 °C and method B corresponds to catalytic conditions in CH_2Cl_2 at 20 °C. [b] Obtained after purification of cycloadduct by column chromatography. [c] Conversion of 80% measured by HPLC.

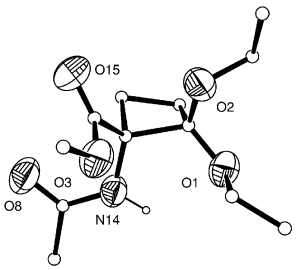
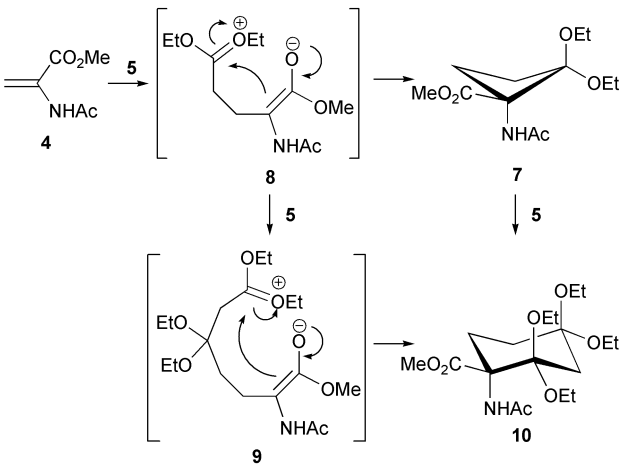


Fig. 1 X-ray structure of compound **7**.



Scheme 2 Mechanism proposed for different reaction conditions.

† Electronic supplementary information (ESI) available: general procedures. See http://www.rsc.org/suppdata/cc/b3/b302000b/

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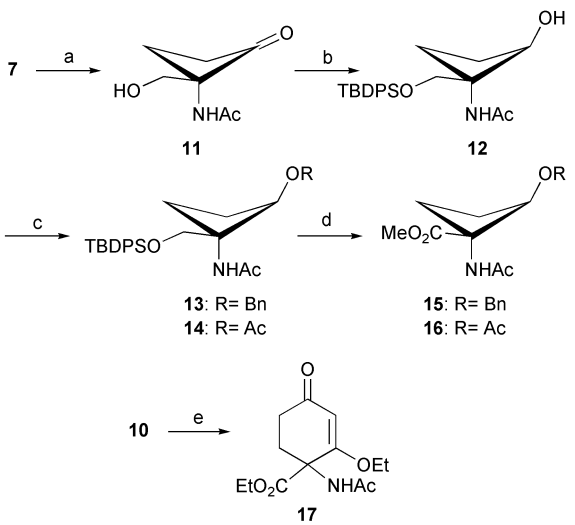
The first addition of one molecule of ketene diethyl acetal **5** onto amidoacrylate **4** by Michael reaction leads to the zwitterion **8**. In the case of thermal conditions this intermediate gives directly the cyclobutane core **7**. Nevertheless, when MAD or MABR are used as the Lewis acid, zwitterion **8** undergoes another ketene diethyl acetal addition to give the zwitterion **9**, which in turn gives the cyclohexane nucleus **10** exclusively, without traces of compound **7**. Moreover, to confirm this mechanism we carried out the reaction of compound **7** with **5** in the presence of MABR and using CH_2Cl_2 as a solvent and after 10 min. at rt, compound **10** was obtained in good yield (Scheme 2).

In order to explore the possible synthetic use of cyclobutane and cyclohexane rings, we developed two synthetic routes. Compound **7** was reduced using $LiBH_4$ to give the corresponding cyclobutanol, which was hydrolysed with HCl to give keto alcohol **11** (Scheme 3).

Protection of the alcohol group with *tert*-butyldiphenylsilyl chloride, followed by hydride addition to the Si face of the carbonyl group, gave alcohol **12** as a single isomer. This compound was assigned unambiguously by X-ray diffraction§. Protection of the secondary alcohol with benzyl 2,2,2-trichloroacetimidate (BTCA), cleavage of the silyl group with TBAF and oxidation in the presence of Jones reagent gave the desired Ac–c_4Ser(OBn)–OH. Purification of this compound was achieved through esterification with CH_2N_2 to obtain, after column chromatography, the pure Ac–c_4Ser(OBn)–OMe (**15**). As an alternative, and in order to increase the yield of the last steps, we protected alcohol **12** as an acetyl ester to give **14**. Compound **16** was obtained from **14** following the same procedure as described above. This scheme represents, to the best of our knowledge, the first synthesis of protected c_4Ser (Scheme 3).

On the other hand, compound **10** was transformed into the interesting building block **17** by simple hydrolysis and further treatment with DBU in EtOH. The position of the OEt group was assigned by NOE experiments. These polyfunctional cyclohexanes can be used as alternatives to Danishefsky's diene in Diels–Alder reactions with 2-acetamido- or 2-benzamidoacrylates[14] to obtain enones with an additional OEt group (Scheme 3).

In conclusion, the absence or presence of bulky aluminium derivatives in the reaction between ketene diethyl acetal and 2-amidoacrylates allows the synthesis of either the cyclobutane skeleton by a [2 + 2] cycloaddition or the cyclohexane framework by a Michael-aldol tandem condensation, adding a new use of Yamamoto catalyst.[15] The use of thermal conditions therefore gives the cyclobutane derivatives **6** and **7**, while catalytic conditions give rise to the unexpected cyclohexane derivative. Both pathways open the door to important compounds, exemplified by the novel Ac–c_4Ser(OBn)–OH. An asymmetric approach to exploit this new reactivity of 2-acylaminoacrylates will be explored in the near future.



Scheme 3 (a) i) $LiBH_4$, Et_2O, rt; ii) 1N HCl, THF/H_2O, rt, 60%; (b) i) TBDPSCl, imidazole, DMF, rt; ii) $NaBH_4$, THF/EtOH, rt, 52%; (c) BTCA, TfOH (cat), Et_2O, rt to obtain **13** or Ac_2O, DMAP, pyridine, rt to obtain **14**; (d) i) TBAF, THF, rt; ii) Jones reagent, acetone, 0 °C; iii) CH_2N_2, Et_2O, rt 20% from **12** in Bn route and 33% from **12** in Ac route; (e) i) THF/1N HCl, rt, ii) DBU, EtOH, rt, 78%.

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Notes and references

‡ *Crystal data*: (a) $C_{12}H_{21}NO_5$, M_w = 259.30, colourless prism of 0.50 × 0.20 × 0.10 mm, T = 293(2) K, orthorhombic, space group $P2_12_12_1$, Z = 8, a = 9.3229(3), b = 13.8767(7), c = 22.3925(9) Å, V = 2896.9(2) Å^3, d_{calc} = 1.189 g cm^{-3}, $F(000)$ = 1120, λ = 0.71073 Å (Mo-Kα), μ = 0.092 mm^{-1}, Nonius kappa CCD diffractometer, θ range 1.91–27.89°, 3068 collected reflections, 3068 unique (R_{int} = 0.000), full-matrix least-squares (SHELXL97, see ref. 16), R_1 = 0.0522, wR_2 = 0.1145, (R_1 = 0.0697, wR_2 = 0.1252 all data), goodness of fit = 1.063, residual electron density between 0.123 and −0.118 e Å^{-3}. Hydrogen atoms were located from mixed methods (electron-density maps and theoretical positions). CCDC 204647. See http://www.rsc.org/suppdata/cc/b3/b302000b/ for crystallographic data in .cif or other electronic format

§ *Crystal data*: $C_{23}H_{31}NO_3Si$, M_w = 397.58, colourless prism of 0.40 × 0.35 × 0.25 mm, T = 173(2) K, monoclinic, space group $P2_1/c$, Z = 4, a = 15.8810(3), b = 8.8310(2), c = 18.6380(4) Å, V = 2238.44(8) Å^3, d_{calc} = 1.180 g cm^{-3}, $F(000)$ = 856, λ = 0.71073 Å (Mo-Kα), μ = 0.127 mm^{-1}, Nonius kappa CCD diffractometer, θ range 1.91–27.89°, 16905 collected reflections, 5311 unique (R_{int} = 0.0392), full-matrix least-squares (SHELXL97),[16] R_1 = 0.0501, wR_2 = 0.1314, (R_1 = 0.0682, wR_2 = 0.1440 all data), goodness of fit = 1.046, residual electron density between 0.642 and −0.334 e Å^{-3}. Hydrogen atoms were located from mixed methods (electron-density maps and theoretical positions) CCDC 204646.

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