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# Solid-phase synthesis of γ-lactams, γ-lactones and cyclobutane derivatives from common resin-bound intermediates

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**Abstract**

Resin-bound cyclobutanone iminium salts, prepared on the solid-phase using the [2+2]-keteneiminium olefin cycloaddition reaction, have been transformed into a number of distinct structural classes including γ-lactams, γ-lactones, cyclobutylamines and cyclobutanols. © 2000 Elsevier Science Ltd. All rights reserved.

*Keywords:* solid-phase synthesis; [2+2] cycloaddition; γ-lactams; γ-lactones; cyclobutylamines; cyclobutanols; cyclobutanones.

Cylobutanones are useful synthetic intermediates for the construction of a wide variety of biologically active carbocyclic and heterocyclic compounds.[1–4] In addition, certain cyclobutanones themselves have been shown to possess some interesting biological properties such as serine protease and β-lactamase inhibition,[5–8] and the cyclobutane ring has been used as a template to mimic more complex structural units of biologically active molecules such as the core of the squalene synthase inhibitor zaragosic acid.[9] Due to recent interest in solid-phase small molecule synthesis[10] we set out to investigate the keteneiminium–olefin cycloaddition as a method to generate cyclobutanones on the solid-phase. Further manipulation of the resulting resin-bound cyclobutanones would allow access to a variety of structurally distinct compounds both through the introduction of different substituents around the central ring and by transformation of the ring itself (Scheme 1).

Commercially available alkenols were immobilised on a carboxylated polystyrene resin **1** which was prepared in three operationally simple steps from Merrifield resin (Scheme 2).[11] The ester-linked alkene resins **2** were added to a five-fold excess of the keteneiminium salts generated in situ from *N*,*N*-dialkylamides according to Ghosez's method,[12] leading to the formation of resin-bound cyclobutanone iminium salts **3** (Scheme 3). Although the iminium species were sufficiently stable to be isolated,† hydrolysis to the corresponding cyclobutanone resin **4** was achieved without any significant cleavage

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† A sample of the resin **3** was stored at room temperature in a screw-capped vial for several weeks without any significant hydrolysis to the corresponding cyclobutanone **4** as observed by on-bead IR.

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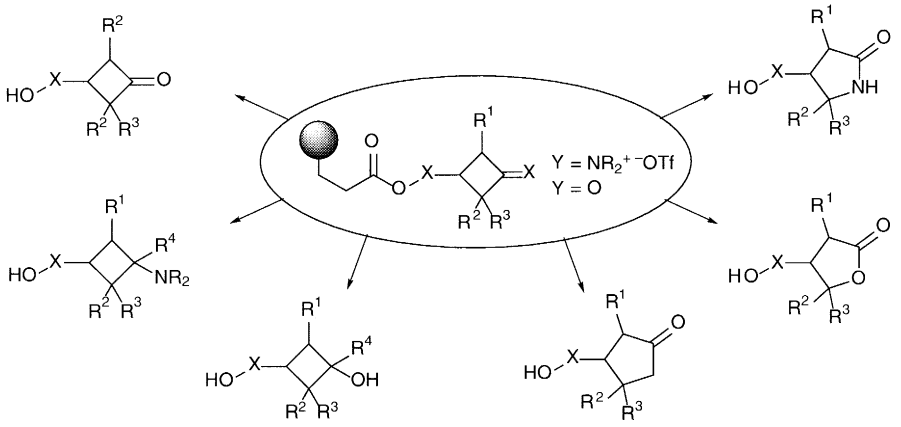
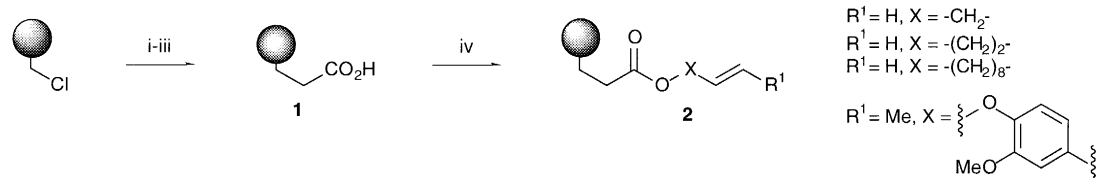
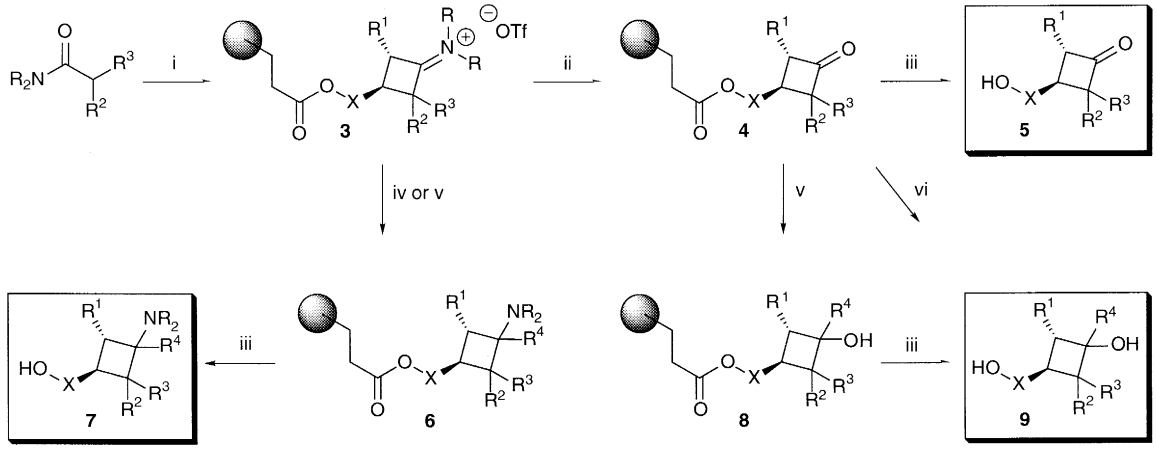



Scheme 1.

of the ester linkage using aqueous $NaHCO_3$ in tetrahydrofuran. The presence of the four-membered ketone was indicated by a carbonyl stretch at around 1770 $cm^{-1}$ in the on-bead IR spectrum. Further evidence that resin-bound cyclobutanones had been prepared was obtained by cleavage from the resin using KOTMS in $CH_2Cl_2$/MeOH to provide the cyclobutanones **5** in high overall yield (see Table 1).[13,14]



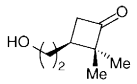
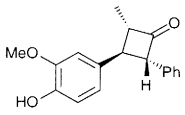
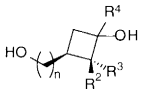
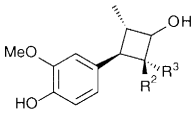
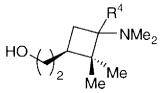
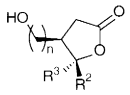
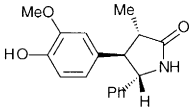
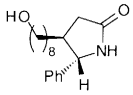

Scheme 2. *Reagents and conditions*: (i) NaH, $CH_2(CO_2Et)_2$, DMF, 60°C; (ii) THF, 2N KOH (aq.) (9:1); (iii) THF, HCl (aq.) (9:1); (iv) alkenol, DIC, DMAP (1 equiv.), $CH_2Cl_2$




Scheme 3. *Reagents and conditions*: (i) $Tf_2O$, $CH_2Cl_2$, 2,6-di-*tert*-butylpyridine, −10°C, then resin **2**, reflux; (ii) THF, $NaHCO_3$ (aq.); (iii) KOTMS, MeOH, $CH_2Cl_2$ or pyrrolidine for phenol **5**; (iv) $Me_4NB(OAc)_3H$, $CH_2Cl_2$; (v) MeMgCl, THF, −78 to −10°C; (vi) $LiBH_4$, MeOH (1 equiv.), THF

Cyclobutylamines **7** and cyclobutanols **9** were also prepared from the resin-bound cyclobutanone iminium species **3** or cyclobutanones **4** as outlined in Scheme 3. In general, the yields of the cycloadducts

Table 1
Products prepared from [2+2] cycloadducts on the solid-phase

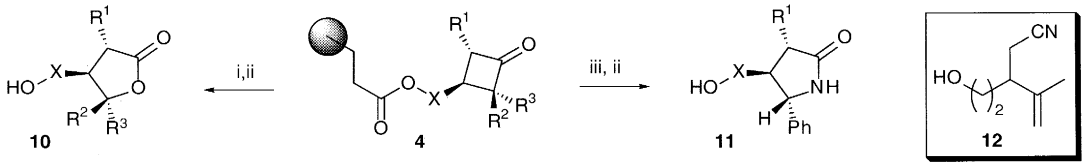
| Entry | Product | n | $R^2$ | $R^3$ | $R^4$ | Yield (%)[a,b,c] |
|---|---|---|---|---|---|---|
| 1 |  | - | - | - | - | 96 |
| 2 |  | - | - | - | - | 38[d,e] |
| 3 |  | 1 | Me | Me | H | 57 (7:1)[c] |
| 4 | | 1 | H | Ph | H | 80[d] |
| 5 | | 2 | Me | Me | H | 70 (5:1)[c] |
| 6 | | 2 | Me | Me | Me | 76 (6:1)[c] |
| 7 | | 2 | H | Ph | H | 94[d] |
| 8 |  | - | Me | Me | - | 84 (3:2)[c] |
| 9 | | - | H | Ph | - | 83 (4:3)[c] |
| 10 |  | - | - | - | H | 97 (13:1)[c] |
| 11 | | - | - | - | Me | 73 (20:1)[c] |
| 12 |  | 2 | H | Ph | - | 88[d] |
| 13 | | 8 | Me | Me | - | 67 |
| 14 |  | - | - | - | - | 67 (10:1)[c] |
| 15 |  | - | - | - | - | 74[d] |

a) All yields refer to isolated products purified by flash chromatography.
b) Yields are calculated based on the loading of the carboxylated resin **1** which was determined by attachment of cinamyl alcohol (DIC/DMAP) followed by cleavage (KOTMS, MeOH, $CH_2Cl_2$) and quantification of cinamyl alcohol released by GC using an internal standard.
c) The figures in parentheses refer to the ratio of the C1 epimers (β:α) which were distinguished by NOE experiments.
d) Only one isomer was observed after flash chromatography.
e) Cleaved from the resin using pyrrolidine.

were superior to the corresponding solution reactions as an excess of the keteneiminium salt was employed to drive the reactions to completion. Nucleophilic addition to the carbonyl or iminium group typically led to a mixture predominating in two diastereoisomers, where the major isomer arose from attack on the α-face of the double bond. Addition of Grignard reagents to the iminium species **3** was noteworthy as an earlier example of the analogous reaction in solution had been reported to be much less efficient,[15] probably due to the presence of impurities in the crude iminium salt from the solution

reaction. The ester linker was not cleaved significantly by methylmagnesium chloride provided the reaction temperature was held below −10°C.

We also examined some ring expansion reactions of the resin-bound cyclobutanones (Scheme 4). Baeyer–Villiger ring expansion of ketones **4** using *m*-CPBA provided γ-lactones **10**, which were cleaved from the resin by transesterification. Similarly, Beckmann rearrangement of **4** ($R^2$=H, $R^3$=Ph) followed by transesterification also proceeded cleanly providing γ-lactams **11**.[16] However, submission of resin **4** ($R^2$, $R^3$=Me) to the same conditions led to the Beckmann fragmentation product **12**.[17]




Scheme 4. *Reagents and conditions*: (i) *m*-CPBA, $CH_2Cl_2$; (ii) KOTMS, MeOH, $CH_2Cl_2$; (iii) *O*-mesitylenesulfonylhydroxylamine, $CH_2Cl_2$, rt

In summary, the [2+2]-keteneiminium olefin cycloaddition has been used to prepare cyclobutanone iminium species on the solid-phase. The resulting resin-bound cycloadducts have been shown to undergo a variety of synthetic transformations, providing products from distinct structural classes cleanly and in high yield. We have noted that the solid-phase reaction offers certain advantages over the analogous solution chemistry. In particular: a higher level of conversion of the olefin is achieved by the use of an excess of the keteneiminium reagent; and purification of the cyclobutanone iminium salt is facilitated by immobilisation on the solid-phase. Our future work focuses on developing practical methods to introduce substituents around the four- and five-membered ring templates described in this paper.

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