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Conjugate intra- and intermolecular addition mediated by methoxide anion on polymeric support

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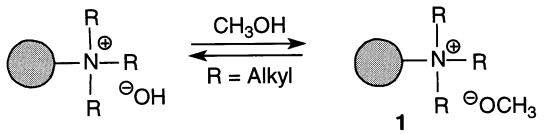
Abstract

By treatment with methoxide anion on polymeric support (IRA 900), chiral β-oxo or β-sulphonyl-amides **2** bearing an α,β-unsaturated ester gave 3,4-disubstituted pyrrolidin-2-ones **3** as easily separable diastereomeric mixtures in good yield and moderate-to-good stereoselection. The polymeric reagent was also effective in promoting both intermolecular conjugate addition and alkylation reactions. © 2000 Published by Elsevier Science Ltd.

As part of a program in medicinal chemistry, we recently required several enantiomerically pure 3,4-*trans*-disubstituted pyrrolidin-2-ones, useful intermediates for both non-proteinogenic amino acids and carbapenems,[1] and we reported the stereoselective synthesis of these compounds by intramolecular conjugate addition[2] requiring anhydrous solvents and air-sensitive reagents.[3–5] However, we considered it important to find more convenient reaction conditions for this preparation; thus, a new route was devised where the enolate anion leading to the conjugate addition could be generated by methoxide anion on polymeric support **1** (Scheme 1).[6–9]



Scheme 1.

The cyclisation reactions were carried out in methanol at 20°C simply by adding the acyclic amides **2a–d** to a suspension of the resin IRA 900 in the methoxide form, **1**[10,11] (Scheme 2).

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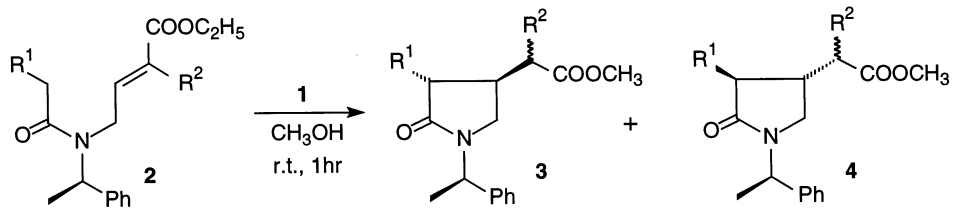
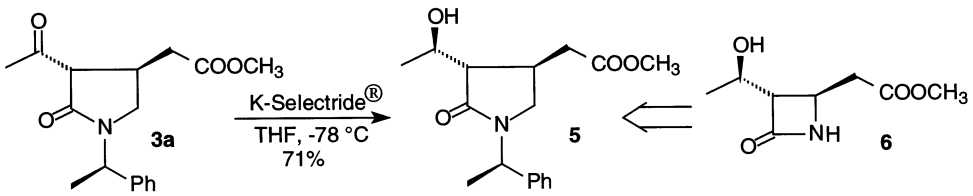


a. $R^1 = CH_3CO$, $R^2 = H$, 75%, d.r. 80:20. **c.** $R^1 = PhSO_2$, $R^2 = H$, 71%, d.r. 68:32.

b. $R^1 = CH_3OOC$, $R^2 = H$, 66%, d.r. 70:30. **d.** $R^1 = PhSO_2$, $R^2 = CH_3$, 77%, d.r. 65:35.

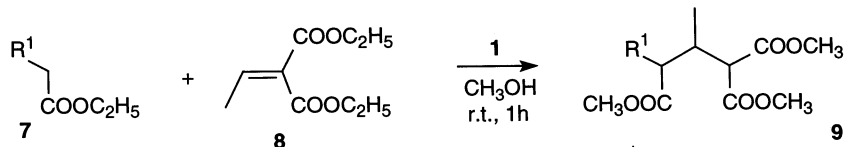
Scheme 2.

The reaction was fast and after 1 h the products were recovered simply by filtering off the polymeric reagent and removing the solvent under reduced pressure.[10] Firstly, it must be pointed out that all the alkoxycarbonyl groups were converted into methoxycarbonyl groups, owing to the transesterificating properties of the polymeric reagent. The choice of the solvent was critical, both ethanol and propanol not being suitable, probably owing to their decreased acidity which does not allow the formation of alkoxide ions. In addition, the temperature was also critical, since at 0°C no reaction was observed. Moreover, the cyclisation proceeded with moderate-to-good stereocontrol, although with a slightly lower stereoselection in comparison with previously reported conditions,[3–5] and the pure diastereomers were isolated by silica gel chromatography. It is worth noting that **3**, the less stable diastereomer, was always the major component of the reaction mixture, in agreement with a kinetically controlled cyclisation process.[5] In a further development, compound **3a** was stereoselectively reduced with K-Selectride® to give the corresponding 3-hydroxyethyl derivative **5**, homochiral with **6**, the precursor of carbapenems[1,10] (Scheme 3).



Scheme 3.

Then, we extended the applicability of methoxide ion on polymeric support **1**, by first considering the intermolecular conjugate addition of stabilised enolate anions to Michael acceptors.[12] In fact, the conjugate addition products **9** were obtained in good yield simply by adding to the polymeric reagent **1**, suspended in methanol, a solution containing **8** together with diethyl malonate or ethyl cyanoacetate, **7a**,**b**, respectively[13] (Scheme 4).



a. $R^1 = C_2H_5OOC$

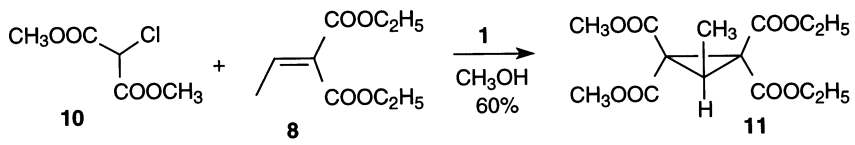
b. $R^1 = CN$

a. $R^1 = CH_3OOC$, 90%

b. $R^1 = CN$, 56%, d.r. 50:50

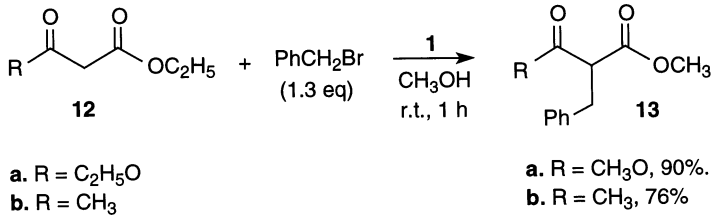
Scheme 4.

Furthermore, when the enolate anion of dimethyl chloromalonate **10** was generated in the presence of **8**, a tandem conjugate addition–S_N2 reaction occurred, leading to the cyclopropyl derivative **11** in moderate yield. In this case, however, transesterification at the ethoxycarbonyl groups was not observed, even on increasing the amount of polymeric reagent **1**[13] (Scheme 5).



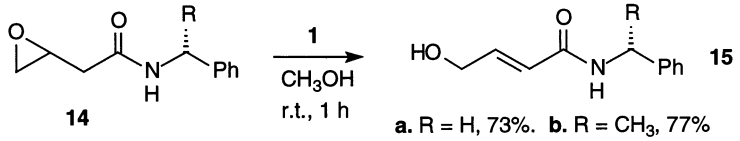
Scheme 5.

Subsequently, in order to test the usefulness of **1** in promoting the formation of enolate anions which could undergo alkylation, a methanolic solution of benzyl bromide and diethyl malonate or ethyl acetoacetate, **12a**,**b**, respectively, was added to the methoxide ion on a polymeric support, **1**, to give the corresponding alkylation products **13** in good yield after filtration, removal of the solvent and column chromatography of the residue[13] (Scheme 6).



Scheme 6.

Finally, a useful application of the polymeric reagent **1** consisted of converting 3,4-epoxy amides **14** into the corresponding *E*-4-hydroxy-2-unsaturated amides **15**. In fact, simply by adding **14** to a suspension of **1** in methanol at rt, the *E*-isomer of **15** was formed exclusively in good yield with excellent stereoselection (Scheme 7).



Scheme 7.

In summary, methoxide anion on polymeric support **1** resulted in an effective generation of enolate anions of β-dicarbonyl esters and amides, which were used to give intra- and intermolecular conjugate addition. The novel features of this methodology are general applicability, mild reaction conditions, avoiding anhydrous solvents and air-sensitive reagents, and simple work-up, which is reduced to a simple filtration of the polymeric reagent. Therefore, the present method can result in useful synthetic organic chemistry and further applications are currently being investigated in our laboratory.

Acknowledgements

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9. Cainelli, G.; Contento, M.; Manescalchi, F.; Regnoli, R. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2516–2519.
10. All new compounds gave satisfactory spectroscopic and high-resolution mass spectra data.
11. Representative experimental procedure for intramolecular conjugate addition: Resin IRA 900 (4.0 g) was added to a solution containing NaOH (4.0 g, 100 mmol) in H_2O (40 ml) at rt. After 30 min, the water was removed and the resin was washed twice with methanol (30 ml). Fresh methanol (50 ml) was then added, and a solution containing **2** (10 mmol) in methanol (10 ml) was added in one portion. After 1 h, the resin was filtered off, the solvent removed under reduced pressure and the residue was purified by flash chromatography (cyclohexane:ethyl acetate 70:30 as eluant).
12. Bergmann, E. D.; Ginsburg, D.; Pappo, R. *Org. React*. **1967**, *10*, 179–555.
13. Representative experimental procedure for intermolecular conjugate addition: To the resin IRA 900 (4.0 g) prepared in methanol (50 ml) as in Ref. 11, were added in one portion **8** (10 mmol) and compound **10** or **12** (10 mmol) dissolved in methanol (10 ml). After 1 h, the resin was filtered off, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (cyclohexane:ethyl acetate 70:30 as eluant).