Report

Soluble Polymer-Bound Allenecarboxylates: Useful β-Ketoester Equivalents

Adel Rafai Far, and Thomas T. Tidwell

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Reports

Soluble Polymer-Bound Allenecarboxylates: Useful β-Ketoester Equivalents

Adel Rafai Far and Thomas T. Tidwell*

Department of Chemistry, University of Toronto, Toronto, Ontario M5S 3H6, Canada

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The importance of heterocyclic compounds to medicinal chemistry has turned these substances into ideal targets for polymer-supported synthesis, especially given the relationship between combinatorial chemistry and drug development.[1] As versatile reagents, β-ketoacid derivatives are very useful substances for the building of heterocycles, and these have been used in a number of polymer-supported syntheses, such as the formation of furans,[2a,b] dihydropyridines,[2c] pyrazolones,[2d,e] dihydropyrans,[2f] pyridines,[2g,h] pyridopyrimidines,[2g] pyridones,[2i] triazoles,[2j] and acyltetramic acids.[2k]

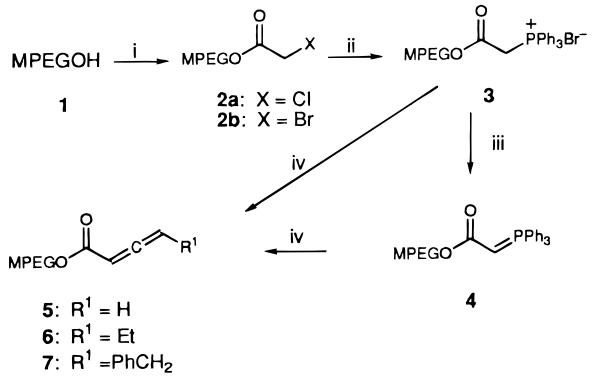
One of the problems associated with these procedures is that the choice of commercially available agents to be used for β-ketoesterification is generally limited to acetoacetylating compounds. Some of these, such as *tert*-butyl acetoacetate,[2d] diketene,[2g] 2,2,6-trimethyl-1,3-dioxin-4-one,[2i] and phenyl acetoacetate,[2j] have already been used in polymer-supported synthesis, but they limit the diversity of the heterocyclic structures produced to those made by a single β-ketoacid derivative. There have been some studies on the derivatization of acetoacetates on a polymeric support[2d,e] to provide more complex β-ketoesters, but this is a complicated task, as one needs to avoid multiple alkylations.

The best available alternative is the use of acyl Meldrum's acids,[2e,h,k] but these are not commercially available and need to be prepared by standard solution chemistry prior to attachment on the support.

Since several of the above-mentioned heterocyclic compounds are prepared via enamines,[2c−e,h−j] which are made via the condensation of amines with the β-ketoesters under dehydrating conditions, and given our own interest in polymer supported cumulenes,[2i] it occurred to us that polymer supported α-allenic esters could efficiently serve as "dehydrated" β-ketoesters. Indeed, amines add to these in a conjugate fashion, to give enamines.[3] These α-allenic esters are readily prepared by the reaction of acid chlorides with stabilized Wittig reagents or with their phosphonium salt precursors, mediated by triethylamine.[4]

Because of the general lack of reactivity of stabilized Wittig reagents bonded to insoluble supports, it was decided that the best choice for a support is the soluble poly(ethylene glycol) monomethyl ether (MPEGOH, **1**),[5] with an average molecular weight of ca. 5000 g mol^{-1}.[6]

Scheme 1[a]



[a] i: DIPEA, XCH_2COX, CH_2Cl_2, room temp. ii: PPh_3, CH_2Cl_2, overnight. iii: CBU, CH_2Cl_2, 45 min. iv: R^1CH_2COCl, TEA, CH_2Cl_2, 2 h.

This polymer was treated with chloroacetyl chloride or bromoacetyl bromide[7] and diisopropylethylamine, chosen over the reported triethylamine as it is less prone to form the quaternary ammonium salt byproduct, and these gave the desired haloacetates (**2a**−**b**), although with some decomposition of the polymer in the case of **2b**, as detected by the integrals in the NMR spectrum. Reaction with triphenylphosphine gives the desired phosphonium salt (**3**) in the case of the bromide **2b**. However, in the case of the chloride **2a** no reaction was observed, even with prolonged reaction times, and higher temperatures eventually led to decomposition. The salt **3** obtained is then converted to the ylid with DBU, giving the desired phosphorane **4**.

This Wittig reagent was reacted with three different acid chlorides in the presence of triethylamine, giving the desired polymer-bound allenes (**5**−**7**) in 87−90% yield (Scheme 1). Alternatively the allenes can be prepared in 89−90% yield directly from the phosphonium salt, by using a larger amount of base.

These allenic esters then readily react with primary amines to give the desired enamines (**8**(**a**−**c**)−**10**(**a**−**c**)), which demonstrates the ability of these polymeric reagents to serve as β-ketoester equivalents. To further illustrate the usefulness of this methodology in the preparation of N-heterocycles, the obtained enamines were converted to 4-pyridones (**11**(**a**−**c**)−**12**(**a**−**c**)) through their reaction with acetyl ketene generated in situ by the thermal decomposition of 2,2,6-trimethyl-1,3-dioxin-4-one,[8] a method which we have already reported to be easily adaptable to soluble polymer-bound chemistry.[2i] In this case, as we previously observed, the bulkier enamines fail to react under these conditions and lead to complex mixtures of products on the support, in which there is no sign of the presence of the pyridones. Cleavage from the support is effected by transesterification to methanol, catalyzed by KCN,[9] giving the 4-pyridones **13**(**a**−**c**)−

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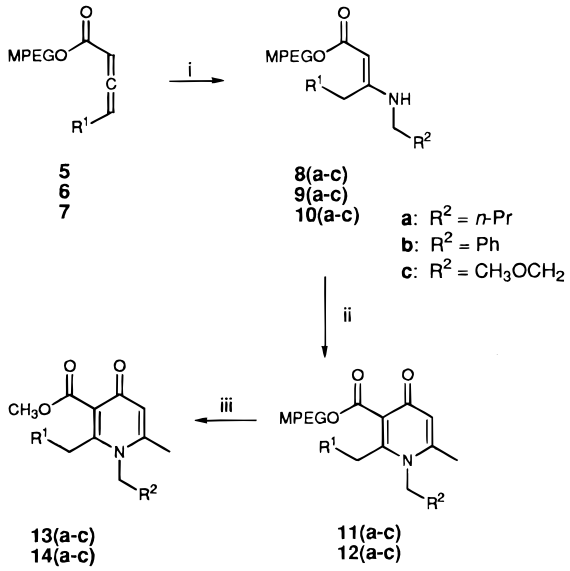
Scheme 2[a]



[a] i: $R^2CH_2NH_2$, CH_2Cl_2, 1 h. ii: 2,2,6-Trimethyl-4*H*-1,3-dioxin-4-one, toluene, reflux 2 h, then repeat. iii: KCN, MeOH, DMF, 60 h.

Table 1. Yields and Purity[a] of Pyridones **8**

compound	R^1	R^2	yield (%)	purity (%)
13a	H	*n*-Pr	74	85
13b		Ph	81	90
13c		CH_3OCH_2	50	86
14a	Et	*n*-Pr	72	92
14b		Ph	60	96
14c		CH_3OCH_2	54	88

[a] Determined by HPLC as the percent area of the peak, detected by absorption at 210 nm.

14(**a**−**c**) (Scheme 2) in good yields and purities after simple filtration through a plug of silica to remove residual MPEGOH (Table 1).

The same enamines can be used with acryloyl imidazole,[10] preformed in the reaction mixture from acryloyl chloride and imidazole, to give the polymer-bound δ-lactams **15**(**a**−**c**) and **16**(**a**−**c**) (Scheme 3). Only the bulkier enamines **9**(**a**−**c**) and **10**(**a**−**c**) were used in the reaction. In this case, the aza-annulation is followed by a shift in the position of the double bond, as it has previously been observed.[11] The reaction also seems sensitive to steric effects, as bulky secondary enamines, such as the ones obtained from 1-phenylethylamine, give little formation of the lactam and instead result in premature cleavage. The product lactams **17**(**a**−**c**) and **18**(**a**−**c**) are released from the support by transesterification followed by chromatography (Table 2). Their structures have been confirmed through 2D NMR experiments on **17b**, including NOESY which confirmed the stereochemistry at the double bond. In the case of compound **17c**, the double bond shifts back into conjugation with the ester upon chromatography.

In summary, soluble polymer-bound α-allenic esters were prepared via the reaction of acid chlorides with stabilized Wittig reagents, and their potential as β-ketoester alternates was demonstrated through the formation of 4-pyridones and δ-lactams.

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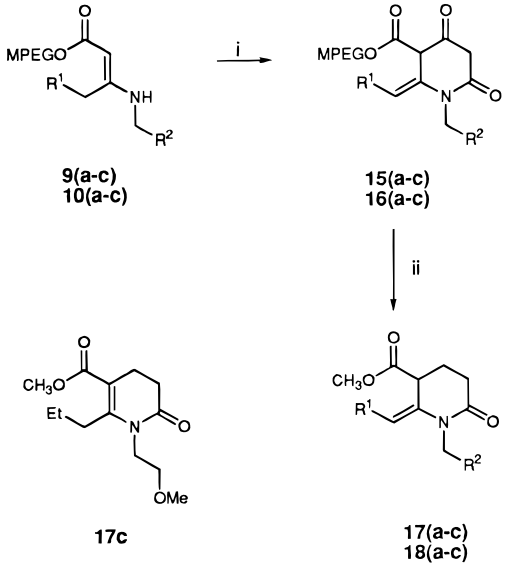
Scheme 3[a]



[a] i: Acryloyl chloride, imidazole, THF, reflux, 20 h. ii: KCN, MeOH, DMF, 60 h.

Table 2. Yields of δ-Lactams **10**

compound	R^1	R^2	yield (%)
17a	Et	*n*-Pr	30
17b		Ph	54
17c		CH_3OCH_2	33
18a	$PhCH_2$	*n*-Pr	29
18b		Ph	46
18c		CH_3OCH_2	36

Supporting Information Available. Experimental procedures and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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