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# SOLID-PHASE SYNTHESIS OF POLYMER-BOUND β-KETOESTERS AND THEIR APPLICATION IN THE SYNTHESIS OF STRUCTURALLY DIVERSE PYRAZOLONES

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**Abstract:** An efficient solid-phase synthesis of different polymer-bound β-ketoesters **7** is described using readily available acid chlorides **1** and haloalkanes **6** as building blocks. The corresponding pyrazolones **9** and **10** were obtained by mild acid catalyzed reaction with phenylhydrazine or by treatment with hydrazine under cyclisation and cleavage from the resin in high purity and good yield. © 1997 Elsevier Science Ltd.

Combinatorial chemistry as a new method for the rapid generation of a great number of structually diverse substances, being required for the high throughput biological screening, is widely recognized to have a great impact on the speed of drug discovery[1,2]. The efforts of preparing these libraries have initiated a high demand for the development of new synthetic transformation on solid support[1,3]. Recent reports of our group describe the use of 1,3-dicarbonyl compounds as a starting material to build up combinatorial libraries via multi-component reactions[4]. We have developed a domino-Knoevenagel-ene reaction on solid phase[5] with polymeric malonate as a substrate to give a great variety of substituted cycloalkanes in good yield and excellent selectivity as well as a polymer-bound three-component domino-Knoevenagel-hetero-Diels-Alder-reaction[6] with polymeric acetoacetate as the substrate to afford structually diverse 3,4-dihydropyrans in good yield and high purity. As part of our studies to prepare diverse β-ketoesters on solid suport, we have previously described the formation of dianions and the γ-alkylation of polymer-bound acetoacetate, as well as the synthesis of C-3 substituted 1-phenyl-pyrazolones[7].

Herein, we report a general method to build up resin-linked β-ketoesters from readily available substrates and their modification by functionalisation of the α-carbon atom. The obtained polymer-bound 1,3-dicarbonyl compounds served as substrates in the preparation of N-1, C-3 and C-4 substituted pyrazolones, which are well known for their widespread biological activity as analgetica, antipyretica, antiphlogistica, antirheumatica, antiarthritica and uricosurica.

Reaction of acid chlorides **1** with Meldrum's acid **2** gave within 2 hours in the presence of pyridine the corresponding acyl Meldrum's acid **3** almost quantitatively[8] (Scheme 1). Heating **3** (5 equiv) with the spacer-modified polystyrene-resin **4**[5] in THF at reflux for 4 hours afforded the polymer-bound β-ketoesters **5** with concomitant release of carbon dioxide and acetone, which helps to drive the reaction to completion (Scheme 1). The reaction could easily be monitored by FT-IR-spectroscopy of the resin (KBr-pellet), which showed in every case a strong appearence of the characteristic C=O streches of β-ketoesters.

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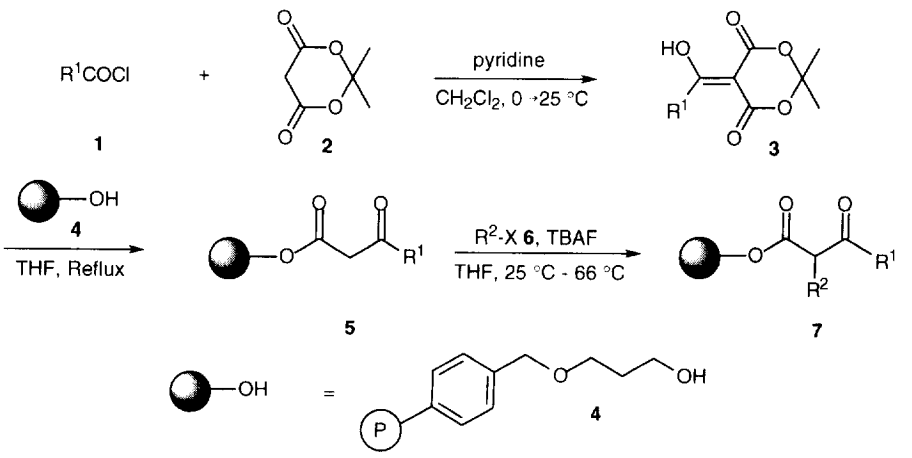
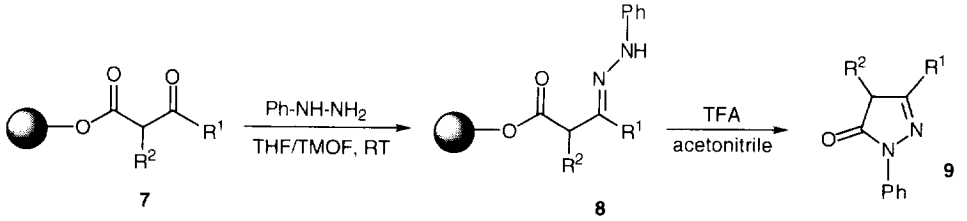
We next turned our attention to the functionalisation at the α-carbon atom of the polymer-bound β-ketoester. Our efforts have led us to establish a protocol for the α-alkylation, which allows the use of an excess of the alkylating reagent and avoids O-alkylation as well as dialkylation. We found that polymeric 1,3-dicarbonyl compounds can easily be alkylated in the α-position at room temperature using the haloalkanes **6** (36 equiv) in the presence of 1 M TBAF[9] in THF (26 equiv, 3 h) to give the β-ketoesters **7** (Scheme 2, Table 1). Only in the case of **7l** higher temperature (66 °C) was required. In all cases it is very important to exclude traces of water, which cause a dramatic decrease of the yield.

**Scheme 1**



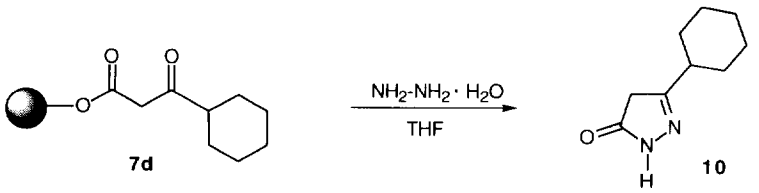

Using the described reaction sequence, a set of the polymer-bound β-ketoesters **7a-l** was synthesized, which was employed directly for the synthesis of the 1-phenyl-pyrazolones **9a-l** according to the following procedure. Addition of an excess of phenylhydrazine (20 equiv, 3 h, 25 °C) in THF / trimethylorthoformate (1 / 1) to the resin-linked β-ketoesters **7a-l** (Scheme 2) gave the 1-phenylhydrazones **8a-l** which cyclize with concomitant release of the final products into the solution under very mild acidic conditions (2 % TFA in acetonitrile, 25 °C) within 0.5 hour to afford the 1-phenyl-pyrazolones **9a-l**[11] in purities from 85-95 %[12](Scheme 2). The overall yield based on the number of free hydroxyl groups in **4**[5] range from 56-95 % (Table 1). Although acetonitrile is a solvent with only modest swelling properties, it was used for the cleavage / cyclisation reaction because it delivered purer compounds in comparison to reactions which were run e.g. in $CH_2Cl_2$.

**Scheme 2**




As an example for the synthesis of N-1 unsubstituted pyrazolones, resin **7d** was treated with hydrazine hydrate (10 equiv) to afford the corresponding pyrazolone **10** in 84 % yield (Scheme 3).

**Scheme 3**




In summary, a general and straightforward method for the synthesis of diverse polymer-bound β-ketoesters starting from acid chlorides and Meldrum's acid has been developed. Moreover, we have described a protocol for the α-alkylation of polymer-bound β-ketoesters using haloalkanes. Since acid chlorides and haloalkanes are readily available from commercial sources, it can be assumed that this generally applicable method will find its broad application in the construction of combinatorial libraries with structually diverse β-ketoesters as the polymeric starting material. The mild conditions of this reaction sequence make it as well amenable for automation. We are currently investigating the great synthetic potential of polymer-bound 1,3-dicarbonyl compounds for the preparation of a variety of other compounds.

**Table 1:** Synthesis of 1-Phenyl-pyrazolones **9**

| **1, 3, 5, 7, 8, 9** | $R^1$ | $R^2$ | X | yield (%)[a] |
|---|---|---|---|---|
| **a** | $CH_2C_6H_5$ | H | / | 91 |
| **b** | $CH_2CH_2CO_2Me$ | H | / | 95 |
| **c** | $CH_2CH_2CH_2Cl$ | H | / | 93 |
| **d** | $C_6H_{11}$ (cyclohexyl) | H | / | 89 |
| **e** | $CH_3$ (see ref.10) | $CH_3$ | I | 64 |
| **f** | $CH_3$ | $C_2H_5$ | I | 58 |
| **g** | $CH_3$ | $CH_2CHCH_2$ | Br | 52 |
| **h** | $CH_3$ | $CH_2CHC(CH_3)_2$ | Br | 81 |
| **i** | $CH_3$ | $(CH_2)_5CH_3$ | I | 80 |
| **j** | $CH_3$ | $CH_2CO_2Et$ | Br | 56 |
| **k** | $CH_2C_6H_5$ | $CH_3$ | I | 76 |
| **l** | $CH_2CH_2CO_2Me$ | $(CH_2)_5CH_3$ | I | 56 |

[a] Yields are based on the concentration of free hydroxyl groups in **4**[5]

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10. Polymer-bound acetoacetate was prepared according to reference 7.
11. All compounds were charaterized by NMR and MS.
12. Purities were determined by NMR.

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