Solid-Phase Synthesis of Substituted Pyrazolones from Polymer-Bound β-Keto Esters

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Dedicated to Professor Dieter Hoppe on the occasion of his 60th birthday

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Polymer-bound acetoacetate **3** was γ-mono- and γ-dialkylated, as well as α-monoalkylated, to give **6**, **9**, and **13**, respectively. Treatment with hydrazine or substituted hydrazines followed by thermal or acidic cyclizing cleavage yielded the pyrazolones **17a–dd** in a purity of >90%.

Introduction

Combinatorial chemistry is generally accepted as a powerful tool in the preparation of a high number of structurally diverse substances for the preparation of lead structures in drug development, catalysts and materials. It can be performed in solution and in the solid state. Here we describe the solid-phase synthesis of pyrazolones in which the formation of the heterocycle occurs at the same time as cleavage from the polymer. With this technique one of the disadvantages of solid-phase synthesis, namely the liberation of the product from the polymer as an additional step, is omitted.[1–6]

Pyrazolones are interesting lead structures since they express high biological activities as analgesics, antipyretics, antiphlogistics, antirheumatics, antiarthritics and uricosurics.[7]

Results and Discussion

For the preparation of a library of diversified pyrazolones,[8,9] the polymer-bound β-keto ester **3** was functionalized employing commercially available alkylating agents and treated with hydrazine or substituted hydrazines. In the investigations we used our modified Merrifield resin **1** which contains a hydroxypropyl ether moiety as spacer.[10] This resin is rather stable and gave the best results in the following transformations; however, Wang resin can also be used. Direct binding of the β-keto ester moiety to the polymer and the use of a longer spacer were less successful. The introduction of the β-keto ester moiety was performed by transacetoacetylation upon heating **1** with *tert*-butyl acetoacetate (**2**) in toluene to give **3**.[11] Various polymer-bound β-keto esters **9** were prepared by treatment of polymer bound **3** with LDA to give the corresponding dianion **4**, which, after removal of unreacted base, was alkylated with a variety of haloalkanes **5**. In these reactions the γ-alkylated β-keto ester monoanions **6** were obtained highly selectively (Scheme 1), and were then transformed into **9** (R^2 = H) by subsequent addition of 2 N HCl and THF (1:1). During the deprotonation the resin changed colour from light yellow to deep red, corresponding to the colour of the dianionic species. In the course of the alkylation the colour fades serving as a convenient indicator for the completeness of the reaction. Transformations with unreactive alkylating agents such as **5a** could easily be driven to completion using an excess of the reagents. Astonishingly, an alkylation at the α-position of the substrate — a usual side product of the synthesis in solution[12] — was not observed even when using a large excess of the alkylating agent. Furthermore, in contrast to the solution chemistry, the addition of HMPTA is not necessary, underlining the advantages of this reaction on a solid support.

Deprotonation of the monoanion **6** with *n*BuLi delivered the new red dianion **7**, which could again be alkylated with different haloalkanes **8** to yield the γ-dialkylated, polymer-bound β-keto ester **9** after protonation with HCl/THF. Thus, two different alkylation agents can be used in this one-pot procedure to give different polymer-bound β-keto esters.

As a second method for the synthesis of polymer-bound β-keto esters, acid chlorides **10** were reacted with Meldrum's acid **11** in the presence of pyridine to give the corresponding acyl Meldrum's acids **12** in almost quantitative yields (Scheme 2). Heating of **12** with the spacer-modified Merrifield resin **1** in THF afforded the polymer-bound β-keto esters **13**, with concomitant release of carbon dioxide and acetone. This transformation can be performed as a two-step procedure in dichloromethane with the interme-

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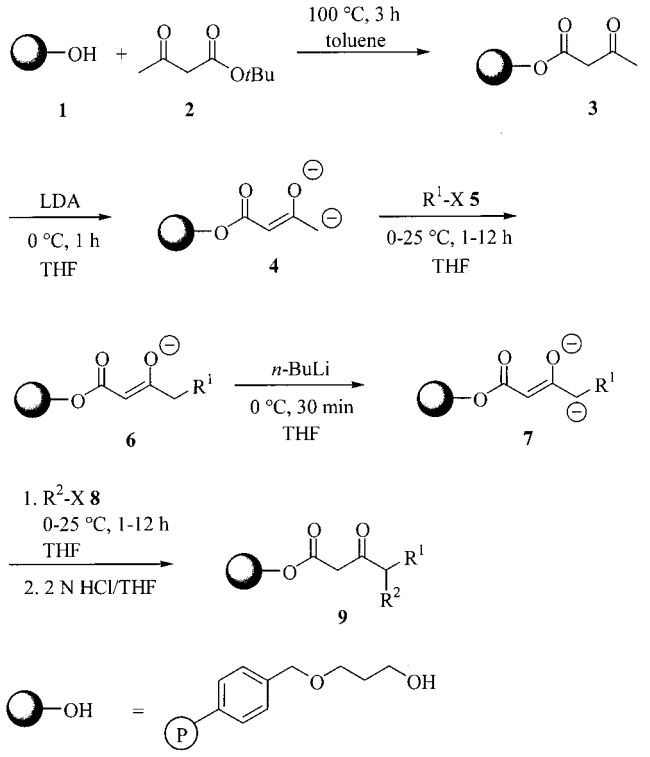
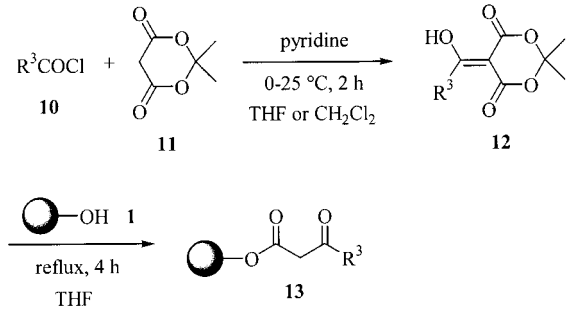


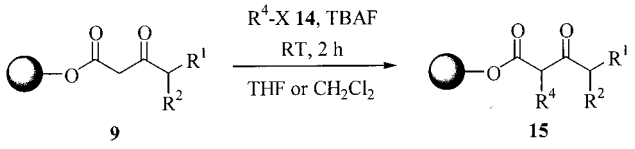
Scheme 1. γ-Alkylation of polymer-bound acetoacetate **3**



Scheme 2. Polymer-bound β-keto esters obtained from Meldrum's acid

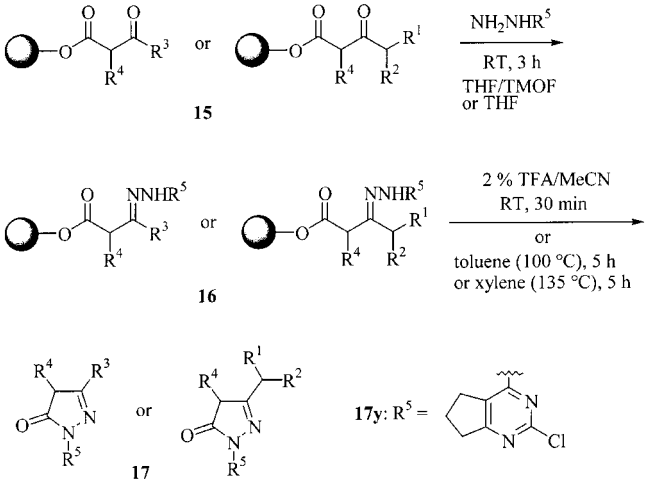
diate aqueous workup of the acyl Meldrum's acids **12**, or more efficiently as a one-pot reaction in THF without isolation of **12**.

To increase diversity we also developed a selective procedure for the synthesis of α-monosubstituted, polymer-bound β-keto esters; α-dialkylated β-keto esters cannot be used for the synthesis of pyrazolones since the formation of the corresponding hydrazones failed. For the synthesis of **15** the polymer-bound β-keto esters **9** were treated with haloalkanes **14** in the presence of 1 M TBAF in THF at room temperature (Scheme 3). It can be assumed that the 1,3-dicarbonyl compound is fixed in its enolic state by forming a very strong hydrogen bond between the fluoride anion and the hydroxyl group;[13] this increases the nucleophilicity of the β-keto ester to allow a C-monoalkylation at room temperature. Thus, O- as well as α,α-dialkylation is prevented by applying these conditions. To obtain good yields, however, it is important to exclude even traces of water. It is also essential to destroy the TBAF complex after the reaction by washing the polymer thoroughly with THF/water, DMF/water and 10% TFA in THF, otherwise the yields and the purity of the products in the following reactions decrease significantly.



Scheme 3. α-Monoalkylation of β-keto esters **9**

Treatment of the substituted polymer-bound β-keto esters **15** obtained by the described procedures with hydrazine or monosubstituted hydrazines gave the corresponding pyrazolones **17** in high yield and excellent purity of >90% (Scheme 4, Table 1−4). In these transformations the hydrazone **16** is formed first and then cyclizes with concomitant cleavage from the polymer, usually at higher temperature. However, in the reaction of hydrazine and **15** the intermediate hydrazone **16** could not be isolated, since it immediately cyclized to give **17** directly at room temperature. Both aliphatic and aromatic compounds can be employed as the substituted hydrazines.



Scheme 4. Formation of the hydrazones and cyclizing cleavage to give the pyrazolones **17a−dd**

Table 1. C-3-substituted 1-phenyl-pyrazolones **17** (R^4 = H, R^5 = Ph) derived from **3** (Scheme 1)

17	R^1-(X) (**5**)	R^2-(X) (**8**)	Yield (%)[a]
a	*i*Pr-(I)	R^2 = H	73
b	$CH_3C(CH_3)CHCH_2$-(Br)	R^2 = H	76
c	$CH_3(CH_2)_9$-(Br)	R^2 = H	60
d	$C_6H_5CH_2$-(Br)	R^2 = H	76
e	$EtO_2CCH_2CH_2$-(Br)	R^2 = H	41[b]
f	2-Br-$C_6H_5CH_2$-(Br)	R^2 = H	62
g	CH_3-(I)	CH_3-(I)	40[c]
h	CH_3CH_2-(I)	$CH_3C(CH_3)CHCH_2$-(Br)	51[c]

[a] Isolated yields are based on the concentration of free hydroxyl groups in **1**.[10] − [b] The crude mixture contains about 30% of unalkylated pyrazolone due to a base-induced elimination of **5e**. − [c] Yields are low due to premature cleavage from the support, probably caused by the excess of *n*BuLi.

Table 2. C-3-substituted 1-phenylpyrazolones **17i**−**l** (R^4 = H, R^5 = Ph) and pyrazolone **17m** (R^4 = H, R^5 = H) derived from **13**

17	R^3	Yield (%)[a]
i	$CH_2C_6H_5$	91
j	$CH_2CH_2CO_2Me$	95
k	$CH_2CH_2CH_2Cl$	93
l	C_6H_{11} (cyclohexyl)	89
m	C_6H_{11} (cyclohexyl)	84

[a] Isolated yields are based on the concentration of free hydroxyl groups in **1**.[10]

As expected, the α-substituted β-keto esters **15** showed a much lower reactivity towards the formation of the polymer-bound hydrazones **16** relative to the corresponding β-keto esters lacking the substituent at the α-position. Quantitative transformations in a relatively short time were nevertheless achieved by using a 1:1 mixture of THF and trimethylorthoformate as reaction medium. Furthermore, more drastic conditions were necessary for the cyclization; thus, the α-substituted hydrazones **16** needed to be heated in xylene at reflux, whereas the reaction of the α-unsubstituted compounds occurred at 100 °C in toluene. However, in view of an automation of the reaction sequence milder conditions would be more suitable. This was achieved by an acid-catalyzed cyclization of the intermediate hydrazone at room temperature within 30 min. using a 2% solution of TFA in acetonitrile; for the formation of **17z** the reaction was performed with TFA in toluene at 80 °C. Though acetonitrile as solvent shows only modest swelling properties, it led to purer compounds than the reactions in dichloromethane, for example. The procedure allowed the synthesis of 1-phenylpyrazolones in a purity of usually >90% with yields of 40−95% (Table 1−4).

Table 3. C-3- and C-4-substituted 1-phenylpyrazolones **17** (R^1 = H, R^5 = Ph) derived from **9** via **15**

17	R^2	R^4-(X) **14**	Yield (%)[a]
n	H	CH_3-(I)	64
o	H	CH_3CH_2-(I)	58
p	H	CH_2CHCH_2-(Br)	52
q	H	$(CH_3)_2CCHCH_2$-(Br)	81
r	H	$CH_3(CH_2)_5$-(I)	80
s	H	EtO_2CCH_2-(Br)	56
t	C_6H_5	CH_3-(I)	76
u	CH_2CO_2Me	$CH_3(CH_2)_5$-(I)	56

[a] Isolated yields are based on the concentration of free hydroxyl groups in **1**.[10]

The structures of the prepared pyrazolones **17a**−**dd** were determined by ^1H and ^{13}C NMR and IR spectroscopy, as well as mass spectrometry. All compounds have a characteristic absorption at $\tilde{\nu}$ = 1710−1730 cm^{-1}, and they all show a strong M^+ peak and a resonance for 4-H at δ = 3.3−3.5 in the ^1H NMR spectrum. As examples, the ^1H and ^{13}C NMR spectroscopic data for **17a**, **17i**, **17s** and **17v** are given in the Experimental Section.[14]

Table 4. *N*-1-substituted pyrazolones **17** (R^3 = Me, R^4 = H)

17	R^5	Yield (%)[a]
v	4-CF_3-Ph	94
w	4-SO_2Me-Ph	96
x	4-NO_2-Ph	55
y	$C_7H_6ClN_2$	54
z	CH_2CF_3	49
aa	2-NO_2-Ph	57[b]
bb	2,4-F_2-Ph	50
cc	Ph-(CH_3)-CH	63
dd	2-Me-cyclohexyl	45

[a] Isolated yields are based on the concentration of free hydroxyl groups in **1**.[10] − [b] The cyclization/cleavage reaction was performed in toluene at 80 °C.

Conclusion

A library of diverse pyrazolones was prepared by binding a β-keto ester unit to a spacer-modified Merrifield resin, followed by γ-mono- or -dialkylation or α-monoalkylation and treatment with hydrazine or substituted hydrazines. A great advantage of this process is the fact that in the course of the formation of the heterocycle a concomitant cleavage from the polymer occurs. In addition, all substrates are readily available from commercial sources, and the mild reaction conditions make the transformation very suitable for automation.

Experimental Section

General: ^1H and ^{13}C NMR spectra: Varian XL-200, VXR-200, and VXR-500; Bruker AMX-300. Chemical shifts were measured in δ (ppm) and coupling constants *J* in Hz. − Mass spectra: Finnigan MAT 95. − Reagents were purchased from Acros, Aldrich, Fluka and Merck and used without further purification unless otherwise noted. Solvents were dried by standard procedures.

Polymer Bound Acetoacetate 3: A mixture of spacer-modified Merrifield resin **1**[10] (10 g, 7.5 mmol, 1.0 equiv.) and *tert*-butyl acetoacetate **2** (12.2 mL, 75.0 mmol, 10.0 equiv.) in toluene (50 mL) was stirred for 3 h at 100 °C. The resin was washed with MeOH and CH_2Cl_2 and dried in vacuo.

General Procedures for the Synthesis of Substituted, Polymer-Bound Acetoacetates 9 and 13. − γ-Monoalkylation: To a 0.45 M solution of LDA in THF (2.5 mL, 1.1 mmol) was added polymer-bound acetoacetate **3** (250 mg, swollen in 5 mL of THF) at 0 °C and the mixture was stirred for 1 h. A change of colour from light yellow to deep red was observed. The solvent with the excess of base was removed with a pipette, the procedure was repeated five times with THF as solvent, and the resin suspended in THF (3 mL). With the more reactive haloalkanes **5b**,**d**,**e**,**f**, addition of two equiv. and stirring for 1.5 h were performed at 0 °C. With the less reactive haloalkanes **5a**,**c**, five equiv. were added at 0 °C and the mixture was stirred for 12 h at room temperature to give the monoanion **6**. During the alkylation reaction the red colour faded. A mixture of 2 N HCl/THF (1:1, 10 mL) was added and the reaction medium stirred for 15 min. The resin was washed with THF, MeOH and THF and dried in vacuo.

γ-Dialkylation: The reaction was performed as described for the γ-monoalkylation and monoanion **6** was washed five times as described above. A 1.6 M solution of *n*BuLi in hexane (1.3 mL, 2.0 mmol, 5.3 equiv.) was added at 0 °C and the mixture stirred for 30 min; the colour of the resin changed to deep red. A haloalkane **8** (2 equiv.) was added and the mixture stirred for 2 h at room temperature. During the alkylation reaction the red colour faded. A 2 N HCl/THF mixture (1:1, 10 mL) was added and the reaction medium stirred for 15 min. The resin **9** was washed with THF, MeOH and THF and dried in vacuo.

Synthesis of Keto Esters with Acyl Meldrum's Acids: To a solution of Meldrum's acid **11** (0.21 g, 1.5 mmol, 4.0 equiv.) in CH_2Cl_2 (40 mL) and pyridine (0.24 mL, 3.0 mmol, 8.0 equiv.) was added acid chloride **10** (4 equiv.) dropwise at 0 °C and the mixture was stirred for 1.5 h at 0 °C and for another 1.5 h at room temperature. The reaction mixture was washed with 1 N HCl (20 mL) and H_2O (10 mL), dried with Na_2SO_4 and the solvent evaporated in vacuo. A solution of the residue **12** (4 equiv.) in THF (5 mL) was added to a suspension of spacer-modified Merrifield resin **1** (0.50 g, 1.0 equiv.) in THF (10 mL) and the mixture was stirred for 4 h at reflux temperature. The resin was washed with THF, DMF, MeOH and CH_2Cl_2 and dried in vacuo.

Polymer-Bound, α-Monosubstituted β-Keto Esters: A mixture of polymer-bound β-keto ester **9** (0.50 g, 1.0 equiv.), 1 M TBAF in THF (5.0 mL, 10 mmol, 26 equiv.) and dry Na_2SO_4 (10 mg) was stirred for 15 min. at room temperature, haloalkane **14** (36 equiv.) added and stirring continued for 2 h at room temperature. H_2O (10 mL) was added and the resin washed with DMF/H_2O (1:1), THF/H_2O (1:1), 10% TFA in THF, DMF, THF, 2-propanole and CH_2Cl_2 and the resin dried in vacuo.

General Procedure for the Synthesis of Polymer-Bound Hydrazones 16. – Method A: The polymer-bound β-keto ester (0.50 g, 1.0 equiv.) was suspended in THF (5 mL), the hydrazine (20 equiv.) added and the mixture stirred for 3 h at room temperature. The resin was washed with THF, toluene and CH_2Cl_2 and dried in vacuo.

Method B: THF/TMOF (1/1) was used as the reaction medium.

General Procedure for the Cyclization/Cleavage of the Polymer-Bound Hydrazones 16. – Method A: The polymer-bound hydrazone (0.50 g, 1.0 equiv.) was suspended in toluene or xylene (10 mL) and stirred for 5 h at 100 °C or 135 °C, respectively. The resin was filtered off, washed with toluene and the filtrate concentrated to dryness (see Table 1–3).

Method B: A mixture of the polymer-bound hydrazone (0.50 g, 1.0 equiv.) and 100 μL of TFA in MeCN (5 mL) was stirred for 30 min. at room temperature. The resin was filtered off, washed with toluene and CH_2Cl_2 and the filtrate was concentrated to dryness to give the desired product.

17a: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.02 (d, *J* = 8.2 Hz, 6 H, *i*Pr-CH_3), 1.99 (sept, *J* = 8.2 Hz, 1 H, *i*Pr-CH), 2.35 (s, 2 H, 1′-H), 3.43 (s, 2 H, 4-H_2), 7.18 (t, *J* = 7.8 Hz, 1 H, *p*-Ph-H), 7.39 (dd, *J* = 7.8, 7.8 Hz, 2 H, *m*-Ph-H), 7.88 (d, *J* = 7.8 Hz, 2 H, *o*-Ph-H). – ^{13}C NMR (50.3 Hz, $CDCl_3$): δ = 22.5 (*i*Pr-*C*H_3), 26.7 (*i*Pr-*C*H), 40.2 (C-4), 42.1 (C-1′), 118.9 (*o*-Ph-C), 125.0 (*p*-Ph-C), 128.8 (*m*-Ph-C), 138.0 (*i*-Ph-C), 159.4 (C=N), 170.6 (C=O).

17i: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.31 (s, 2 H, 4-H), 3.81 (s, 2 H, CH_2Ph), 7.05–7.59 (m, 8 H, Ph-H), 7.88 (d, *J* = 7.8 Hz, 2 H, *o*-Ph-H). – ^{13}C NMR (50.3 Hz, $CDCl_3$): δ = 37.9 (*C*H_2Ph), 41.1 (C-4), 118.9 (*o*-Ph-C), 125.1 (*p*-Ph-C), 127.4 (*p*-Ph-C′), 128.79 (*m*-Ph-C′), 128.84 (*m*-Ph-C), 129.0 (*o*-Ph-C′), 135.5 (*i*-Ph-C′), 138.0 (*i*-Ph-C), 158.6 (C=N), 170.5 (C=O).

17s: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.28 (t, *J* = 7.5 Hz, 3 H, CH_2CH_3), 2.13 (s, 3 H, 3-CH_3), 2.91–2.96 (m, 2 H, 1′-H), 3.58 (m_c, 1 H, 4-H), 4.15 (q, *J* = 7.5 Hz, 2 H, CH_2CH_3), 7.18 (t, *J* = 7.8 Hz, 1 H, *p*-Ph-H), 7.39 (dd, *J* = 7.8, 7.8 Hz, 2 H, *m*-Ph-H), 7.88 (d, *J* = 7.8 Hz, 2 H, *o*-Ph-H). – ^{13}C NMR (50.3 Hz, $CDCl_3$): δ = 14.0 (CH_2CH_3), 16.0 (3-CH_3), 33.9 (C-1′), 58.3 (C-4), 61.4 (CH_2CH_3), 118.3 (*o*-Ph-C), 124.5 (*p*-Ph-C), 128.9 (*m*-Ph-C), 138.0 (*i*-Ph-C), 159.1 (C=N), 170.0 (C=O), 172.1 (C=O).

Synthesis of the *N*-Unsubstituted Pyrazolone 17: To a suspension of β-keto ester **13** (R^3 = cyclohexyl; 0.20 g, 1.0 equiv.) in THF (3 mL) was added hydrazine hydrate (10 equiv.) and the mixture stirred for 2 h at room temperature. The resin was washed with THF and the unreacted hydrazine hydrate removed by filtration over SiO_2. The solution was then concentrated to dryness (see Table 4).

Synthesis of *N*-1-Substituted Pyrazolones 17: Polymer-bound β-keto ester **3** (0.50 g, 1.0 equiv.) was condensed with hydrazines NH_2NHR[5] (20 equiv.) to give the corresponding hydrazones **16** following the general procedure, method A. The cyclization/cleavage was performed following the general procedure, method B (see Table 4).

17v: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.23 (s, 3 H, 3-CH_3), 3.06 (s, 3 H, SO_2CH_3), 3.50 (s, 2 H, 4-H_2), 7.93 (d, *J* = 9.4 Hz, 2 H, *m*-Ph-H), 8.15 (d, *J* = 9.4 Hz, 2 H, *o*-Ph-H). – ^{13}C NMR (50.3 Hz, $CDCl_3$): δ = 17.0 (3-CH_3), 43.1 (C-4), 44.6 (SO_2CH_3), 118.1 (*o*-Ph-C), 128.3 (*m*-Ph-C), 135.4 (*p*-Ph-C), 142.2 (*i*-Ph-C), 157.5 (C=N), 170.9 (C=O).

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