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Solid-phase aldol condensations mediated by zinc acetate and 2,2′-bipyridine under weakly basic conditions

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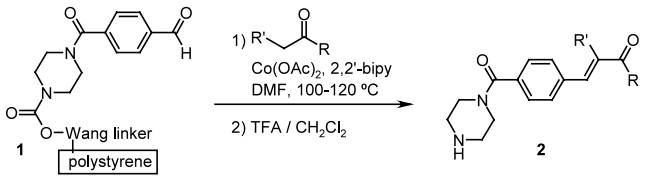
Abstract—A new, efficient and convenient method for the synthesis of resin-bound α,β-unsaturated ketones is described. Reaction of polystyrene-linked benzaldehydes with methyl ketones or tetralone in the presence of zinc acetate, 2,2′-bipyridine and an amidine base at elevated temperature gave resin-bound (*E*)-enones in high purity. These were transformed into thioethers by reaction with thiophenol.

The synthesis of organic molecules on insoluble supports is a widely used tool for combinatorial and parallel production of compound libraries. Crossed aldol condensation of ketones with aldehydes is considered to be very useful in this context, since a highly diverse set of starting materials are commercially available and the resulting α,β-unsaturated ketones are versatile intermediates for a large variety of compound classes. Examples of solid-phase aldol additions and condensations have been described,[1–3] usually employing either protic solvents, suspensions or very strong bases. If excess ketone is used in a base-catalysed aldol condensation, undesired Michael addition of the ketone to the resulting enone can occur.[1,2] Marzinzik and Felder reported aldol condensations of a resin-bound benzaldehyde with acetophenones in excellent purities and yields, using a suspension of LiOH in dimethoxyethane.[2] This procedure led to incomplete reaction in our hands and may also be incompatible with some ester-based linkers. In this letter, a new variant of an aldol condensation suitable for parallel solid-phase synthesis is reported. The method affords support-bound α,β-unsaturated ketones ready for further derivatisation on solid phase.

As early as in 1980, Irie and Watanabe described solution phase aldol condensations of excess enolisable ketones with aromatic aldehydes in the presence of cobalt(II) or zinc acetate 2,2′-bipyridine complexes.[4] This method did not gain broad use due mainly to the large excess of one reactant needed, the need for high temperature and the variety of alternative ways of performing aldol reactions in solution. However, some advantages of the Irie–Watanabe procedure are that the reagents can be added as solutions and no prior transformation of the ketone is necessary. The reaction proceeds without requiring dry or inert conditions, and the corresponding α,β-unsaturated ketones are obtained directly in a reasonable yield without Michael addition by-products. These features make the reaction interesting from a 'combinatorial chemist's' point of view.

The adoption of the Irie–Watanabe protocol[4] to solid-phase conditions was investigated first. Thus, the polystyrene-bound benzaldehyde **1** on a Wang carbamate linker[5] was treated with several methyl ketones and 1-tetralone in the presence of cobalt(II) acetate and 2,2′-bipyridine in DMF at 115–120°C for 20–25 h. After washing and subsequent cleavage from the polystyrene resin with trifluoroacetic acid (TFA), the corresponding enones **2** were detected in 70–98% purity by LCMS/evaporative light scattering (ELS) detector (Scheme 1).[6]

After these encouraging results, milder reaction conditions seemed to be desirable. Irie and Watanabe suggested a mechanism in which the metal ion is complexed by the bipyridine and the ketone and the acidity of the ketone is increased by this complex formation. The acetate ion is believed to act as a base



Scheme 1.

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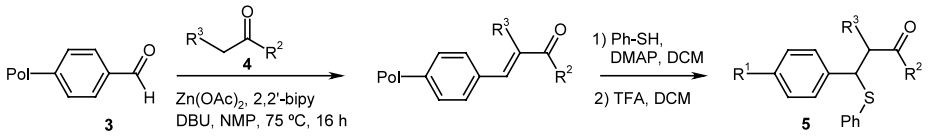


Scheme 2.

which partially transforms the complexed ketone into an enolate anion.[4] If this hypothesis is correct, addition of a stronger base than acetate should promote the reaction **1→2**, as long as formation of the metal–ketone–bipyridine complex is not impeded. Indeed, it was found that the reaction rate is enhanced in the presence of the amidine base DBU, though elevated temperatures are still necessary for completing the reaction. DBU alone, without any metal salt added, did not catalyse this aldol reaction. The mechanism suggested by Irie and Watanabe[4] is confirmed by these results. Cobalt(II) acetate and zinc acetate gave equal results although zinc acetate is clearly a better choice because it is less harmful and cheaper than cobalt(II) acetate. DMF could be successfully replaced with the less toxic *N*-methylpyrrolid-2-one (NMP).

The following procedure for aldol condensations of resin-bound benzaldehydes with methyl ketones or tetralones is recommended: to the aldehyde resin (0.03 mmol), a solution of the ketone (1.2 mmol) in NMP (0.8 ml) was added, followed by a solution of zinc acetate dihydrate (0.05 mmol) and 2,2′-bipyridine (0.05 mmol) in NMP (0.25 ml) and a solution of DBU (0.05 mmol) in NMP (0.1 ml). The mixture was shaken at 75°C for 16 h. The resin was washed with NMP, methanol and dichloromethane to afford the resin-bound enone.

This procedure was used for the reaction of polystyrene-bound benzaldehydes **3** with ketones **4**. The starting materials **3** were prepared in the following manner: aldehyde **3a**[2] from commercially available Rink amide resin[7] (*Novabiochem* 01-64-0013; removal of the Fmoc protecting group with 20% piperidine in DMF, followed by overnight *N*-acylation with a 2:1 mixture of 4-formylbenzoic acid and *N*,*N*′-diisopropylcarbodiimide [DIC] in dichloromethane/NMP 3:2), aldehyde **3b**[8] from commercially available Wang resin[9] (*Bachem* D-1250; *O*-acylation with 4-formylbenzoic acid, DIC and a catalytic amount of 4-dimethylaminopyridine in 1,2-dichloropropane/NMP 1:2 for 6 h, similarly to a procedure reported for the reaction of Wang resin with cyanoacetic acid[10]) and aldehyde **3c** from commercially available 2-chlorotritylchloride polystyrene resin (*Novabiochem* 01-64-0103; reaction with a 1:2 mixture of 4-hydroxybenzaldehyde and ethyldiisopropylamine in 1,2-dichloropropane/NMP 1:2 for 6 h). After reaction of aldehyde resins **3** with ketones **4**, the resulting resin-bound enones were transformed into thioethers **5** by subsequent addition of thiophenol. These were cleaved from the resin and analysed (Scheme 2, Table 1). The thiophenol addition was included in order to distinguish between aldol condensation on the resin and aldol addition, since some aromatic aldol addition products can give the corresponding enones during the final treatment with TFA.

As indicated by the examples shown in Table 1, acetophenones, tetralone and aliphatic methyl ketones are suitable for this aldol condensation. Reaction of the Rink-resin-bound aldehyde **3a** with acetophenone, 2,4-dimethoxyacetophenone and propiophenone (entries 1, 2 and 8) gave similar results as reported for the LiOH based procedure by Marzinzik and Felder.[2] Propiophenone did not react with the aldehyde (entry 8). The ketone can also be a phenol (entry 3) or a carboxylic ester (entry 6). Michael addition to the enone only occured with a very electron-deficient acetophenone (entry 5). Reaction of pyran-4-one with aldehyde **3a** caused partial cross-linking on the resin (entry 9, product **6**). Both ester and 2-chlorotrityl phenyl ether linkage of the aldehyde **3** were suitable for the aldol reaction conditions (entries 12 and 13). However, aldehyde **3c** did not give the thioether **5**, affording the corresponding enone instead after cleavage from the resin. Thus, it is not clear whether the elimination step proceeded on the resin or upon TFA treatment (entry 13).

In two cases (entries 1 and 10 in Table 1),[†] the corresponding enones **7** and **8** were cleaved from the resin

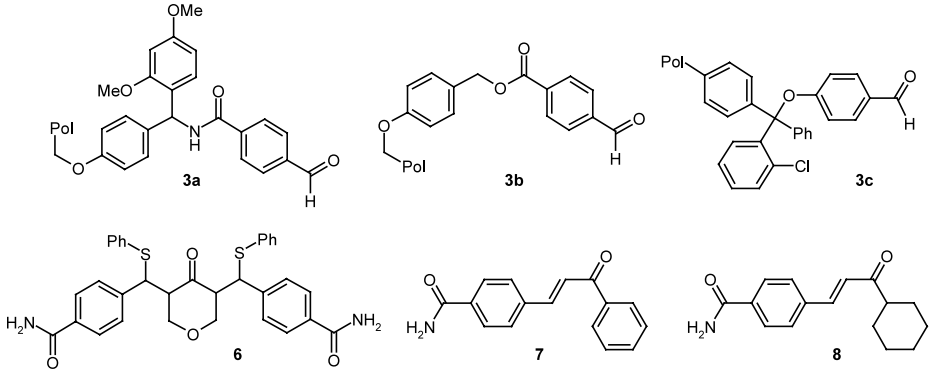
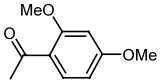
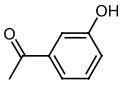
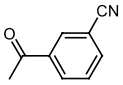
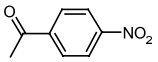
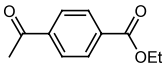
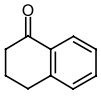
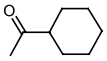
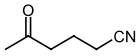


Table 1. Synthesis of thioethers **5** from aldehydes **3** and ketones **4**

Entry	Aldehyde **3**	Ketone **4**	R^1 in structure **5**	Purity of **5** (%)[a]	Yield of **5** (%)[b]	Other products (purity)[a]
1	**3a**		H_2N-CO-	90	54[c]	
2	**3a**		H_2N-CO-	80	34[c]	
3	**3a**		H_2N-CO-	96	64[d]	
4	**3a**		H_2N-CO-	75	43[d]	
5	**3a**		H_2N-CO-	47	36[c]	32 % Michael adduct[e]
6	**3a**		H_2N-CO-	90	54[c]	
7	**3a**		H_2N-CO-	97	70[c]	
8	**3a**		H_2N-CO-	traces	<1[c]	starting aldehyde[f]
9	**3a**		H_2N-CO-	20	3[c]	unidentified products 13 % compound **6**[e]
10	**3a**		H_2N-CO-	79	40[c]	
11	**3a**		H_2N-CO-	90	34[d]	
12	**3b**		HO-CO-	89	40[c]	
13	**3c**		HO-	0	0[c]	87 % enone in 52 %[c] yield

[a] By LCMS/ELS detector.
[b] Detected in the crude product; reaction sequence including attachment of the aldehyde to the resin.
[c] Yield estimation by means of ELS detection as described in footnote.†
[d] By ^{1}H NMR in DMSO-d_6 with DMSO-d_5 as internal standard.
[e] Structural proposal based on LCMS.
[f] Front peak in HPLC; amount of aldehyde not determined.

with TFA and analysed by ^{1}H NMR in DMSO-d_6. Only (*E*) configured products were detected in both cases: the alkene protons of crude enone **7** gave doublets at 7.78 and 8.05 ppm with a coupling of 15.7 Hz; the corresponding doublets of compound **8** appeared at 7.13 and 7.60 ppm with a coupling of 15.7 Hz. The stereochemistry of the thioethers **5** was not investigated.

† It is assumed that, for non-volatile compounds, the area of an ELS peak in a chromatogram directly correlates with the mass concentration of the corresponding compound.[11] For all entries in Table 1, the crude product mixtures were equally diluted and analysed with LCMS/ELS. Additionally, for entries 3 and 4 in Table 1, the absolute amounts of products **5** were determined by ^{1}H NMR spectroscopy with an internal standard, and the results were compared with the ELS peak areas obtained by LCMS/ELS. Thus, an average correlation factor for the connection between the mass concentration of the thioether **5** and the area of the corresponding ELS peak was established. This correlation factor obtained from entries 3 and 4 was used to calculate the amount of thioether **5** or enone from the area of the corresponding ELS peak in the chromatogram.

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