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Tetrahedron Letters 44 (2003) 1067–1069

TETRAHEDRON LETTERS

Solid-phase synthesis of traceless 1,3-diketones

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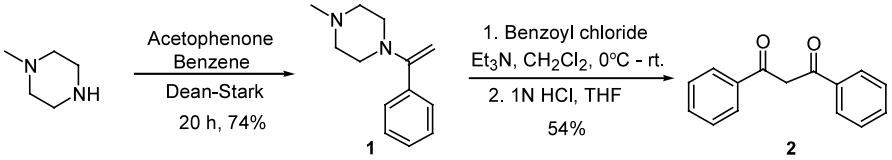
Received 22 October 2002; revised 25 November 2002; accepted 25 November 2002

Abstract—A traceless synthesis of 1,3-diketones has been achieved through enamine methodology from solid-phase organic synthesis. Thus, piperazine served as a linker for this traceless cleavage of β-diketones from solid support.

1,3-Diketones are important intermediates not only as a key building block for the synthesis of core heterocycles such as pyrazole,[1] isoxazlole,[2] and triazole[3] in medicinal chemistry, but also as an invaluable chelating ligand for various lanthanide and transition metals in material chemistry.[4] Although there are many reports of the synthesis of 1,3-diketone scaffold and its derivatives from solution phase chemistry,[5] few routes using solid-phase are known, and these routes need some improvements for our purpose. For example, 1,3-diketone scaffold has been constructed in Wang or Rink amide resin through Claisen condensation, providing a starting material for pyrazole and isoxazole based heterocycle libraries.[6] However, that method, upon cleavage from solid-phase, resulted in unwanted tether such as amide[6i] or hydroxy[6ii] functional group in the product depending on the resin used. This unwanted functional group attached to the 1,3-diketones negatively influences the formation of β-diketone-metal complexes for various materials. Furthermore, application to the synthesis of various heterocycles can result in biologically undesirable functionality in the final products. Thus, a traceless synthetic strategy for 1,3-diketones needs to be developed to provide a large number of diverse 1,3-diketones from solid-phase combinatorial approach. To achieve this end, we examined enamine methodology.[7] Morpholine or pyrrolidine is widely used for the formation of ketone enamine, which, upon reaction with acyl halide, followed by hydrolysis, affords β-diketones. Since polymer supported piperazine is commercially available we chose to explore its use as a linker for enamine acylations. One example of using piperazine as a linker has been reported for the synthesis of α,β-unsaturated methyl ketones.[8] A preliminary solution phase reaction showed that β-diketone **2** was obtained from *N*-methylpiperazine through its enamine intermediate **1** (Scheme 1).

This result convinced us to further explore commercially available polymer bound piperazine **3** in this reaction. Thus, several methyl ketones were attached to piperazinomethylpolystyrene through azeotropic dehydration to afford enamine bound polymer **4**. Subsequent reaction of this polymeric enamine intermediate with substituted acyl halides provided acylated enamines **5**. After acid hydrolysis of the polymer bound acylated enamine, traceless β-diketones **6** were obtained (Scheme 2).[9]

It is known that halogen (especially fluorine) containing β-diketones are in many instances superior intermedi-



Scheme 1.

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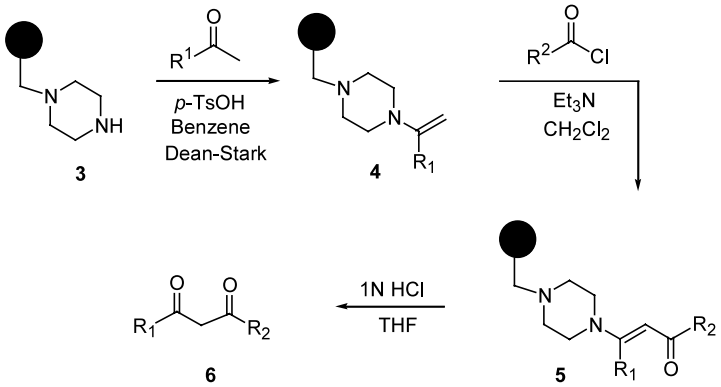
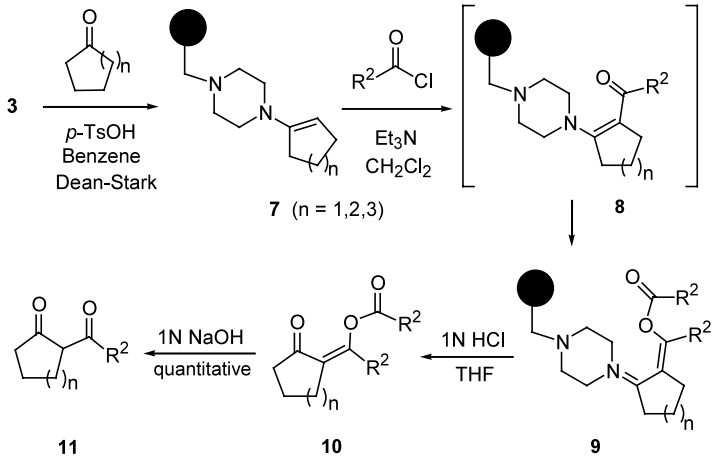


Scheme 2.



Scheme 3.

ates to their non halogenated (fluorinated) analogues for their useful properties such as metal extraction or high biological activities.[10]

Enamine bound resin **7**, which was made from cycloalkanones, provide polymer bound enol ester **9** exclusively when reacted with electron withdrawing group substituted acyl halides. The released enol ester **10** from hydrolysis of the resin **9** was quantitatively safonified to afford desired β-diketones **11** (Scheme 3 and Table 1).

Enol ester **10** is also known as an invaluable intermediate for the synthesis of functionalized furan derivatives by McMurry-type coupling reaction[11], and we are currently exploring this reaction from solid-phase chemistry.

In summary, we have established a viable route for the traceless solid-phase synthesis of 1,3-diketones via enamine methodology. This is the first report for the synthesis of traceless 1,3-diketones from solid-phase, and production of a large library of this scaffold via parallel solid-phase synthesis is currently underway.

Acknowledgements

We thank Dr. Patricia L. Watson for the full support to this research and Dr. Steven W. Shuey for comments on the manuscript.

Table 1. 1,3-Diketones (**6** or **11**) from solid-phase

Entry[a]	R^1 or n	R^2	Yield[b] (%)
6-1	C_6H_5-	C_6H_5-	36
6-2	C_6H_5-	*o*-F-C_6H_4-	53
6-3	C_6H_5-	*p*-CF_3-C_6H_4-	40
6-4	C_6H_5-	C_6F_5-	42
6-5	*p*-CH_3-C_6H_4-	*p*-Cl-C_6H_4-	29
6-6	*p*-F-C_6H_4-	C_6H_5-	38
6-7	Biphenyl	C_6H_5-	57
11-1	$n=1$ (Cyclopentane)	*p*-F-C_6H_4-	35
11-2	$n=2$ (Cyclohexane)	*o*-Cl-C_6H_4-	66
11-3	$n=3$ (Cycloheptane)	*p*-F-C_6H_4-	50

[a] All known compounds.
[b] Overall yield after purification from short silica column chromatography.

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9. Typical procedure (Table 1, entry **11–2**): Resin **3** (5 g, 5.4 mmol, loading: 1.08 mmol/g; purchased from Argonaut Technologies) was treated with cyclohexanone (10.6 g, 108 mmol, 20 equiv.) and *p*-TsOH (40 mg, 0.21 mmol) in benzene (80 mL). The reaction mixture was refluxed for 24 h using 4 Å molecular sieve containing Dean–Stark apparatus under nitrogen. The resin was washed with dried benzene (30 mL×5) under nitrogen, and put under vacuum to afford 5.4 g of desired resin **7** ($n=2$) (FTIR (KBr): 1682 cm^{-1}). To the suspension of resin **7** ($n=2$) (1 g, 1 mmol/g) in DCM (20 mL) was added Et_3N (2 mmol, 0.28 mL), followed by the addition of 2-chlorobenzoyl chloride (2 mmol, 0.18 g). The reaction mixture was stirred at rt overnight. The resin was filtered, washed with DCM (20 mL×3), and treated with THF/1N HCl (6 mL/1 mL) for 20 min at rt. After filtration of the resin, the filtrate was concentrated under Genvac to afford enol ester **10** ($n=2$), which was finally saponified (THF/1N NaOH = 6 mL/1 mL) at rt for 4 h. Sequential neutralization (1N HCl, pH 7), concentration under Genvac, and short silica column chromatography afforded 1,3-diketone **11-2** as a white solid (150 mg). Yield (overall): 66%, mp: 64°C (enol tautomer), FTIR (KBr): 1595 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$): δ 15.86 (s, 1H), 7.41–7.38 (m, 1H), 7.35–7.31 (m, 2H), 7.23–7.21 (m, 1H), 2.46 (t, 2H, $J=6.4$ Hz), 2.07 (t, 2H, $J=6.1$ Hz), 1.73 (m, 2H), 1.59 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.2, 187.9, 137.6, 130.7, 130.1, 128.0, 127.9, 127.3, 108.4, 32.5, 24.8, 23.2, 22.0. Anal. calcd for $C_{13}H_{13}ClO_2$: C, 65.97; H, 5.54; Cl, 14.98. Found: C, 65.77; H, 5.38; Cl, 14.91.
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