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The regioselective preparation of 1,3-diketones

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Abstract—The regioselectivity of the acylation of Li enolates and silyl enol ethers is reported using acyl halides and acyl cyanides. We illustrate a simple method for the preparation of 1,3-diketones via the silyl enol ether in excellent yields, free from competing *O*-acylation and diacylation products.

The enolate has been described as the most important intermediate in C–C bond formation. Its ambident nature however, allows the formation of bonds at either the carbon or the oxygen. In the case of acylation, this can result in the undesirable formation of a mixture of *O*- and *C*-acylated products which are difficult to separate, often resulting in low yields.[1] A large amount of work has been undertaken in order to explore and understand the reaction conditions that promote the regioselective acylation of enolates, these include; the nature of the counterion, reaction temperature, solvent, stoichiometry of reagents, order of reagent addition and type of acylating reagent.[2,3] Although careful selection of the aforementioned conditions has been shown to influence the regioselectivity of the acylation, the 1,3-diketones produced remain contaminated with small amounts of *O*-acylated product.[4,5] The procedure is still therefore regarded as being heavily substrate dependant.[6]

In the late 1960s, Stork et al. demonstrated that an enolate could be transformed into a silyl enol ether and then converted back to the enolate.[6] The technique therefore enables the temporary trapping of an enolate while maintaining the regio- and stereochemical features.[7,8] Stork described the regeneration of enolates via the use of methyllithium. However, more recently *anhydrous* fluoride salts[9] and reagents such as potassium ethoxide[10] have found use in desilylation reactions. Beck et al. demonstrated the *C*-acylation of Li enolates generated by the treatment of silyl enol ethers with methyllithium.[11] This technique proved advantageous as it removed the undesirable reaction between the acylating reagent and amide base (LDA), previously observed by Rathke et al.[2] Howard and co-workers[12] have also demonstrated the *C*-acylation of Li enolates (generated using LDA) using acyl cyanides.[13,14] Using this methodology, no competing *O*-acylation, diacylation or reactions of the enolate with the cyanide group were reported.

Although many techniques have demonstrated the formation of C–C bonds via the use of Li enolates and silyl enol ethers, there are few that enable the preparation of clean *O*-acylated products. Noyori et al. however demonstrated the selective *O*-acylation of silyl enol ethers using stoichiometric amounts of the expensive fluoride source, tris(dimethylamino)sulfonium difluorotrimethyl silicate (TASF).[15] Limat and co-workers, subsequently demonstrated the use of a catalytic amount of tetrabutylammonium fluoride trihydrate to afford enol esters in good yields.[16]

We report here a simple procedure for the regioselective acylation of ketones from their respective Li enolates (prepared using LiHMDS)[17] and silyl enol ethers[18,19] using a series of acylating reagents. The enolates are regenerated from the silyl enol ethers using a catalytic amount of *anhydrous* TBAF.[20] This effectively means that the enolate formed is 'naked' i.e. remains relatively unaffected by its counterion, in this case the 'soft' ammonium ion.[7] As Table 1 illustrates, the products were isolated in good to excellent yields.

As Table 1 illustrates, the acylation of the Li enolate of acetophenone with acetyl chloride results in the formation of the *O*-acetylated product **1**.[21] *O*-Acylation **3**[23] was also observed when using the reagent benzoyl chloride (Table 1), no contamination from competing

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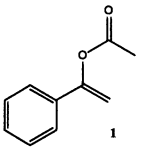
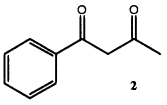
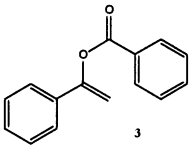
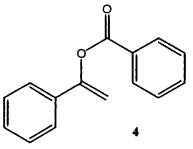
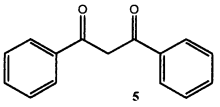
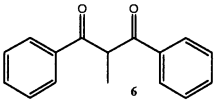
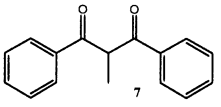
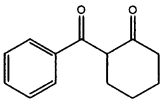
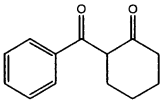
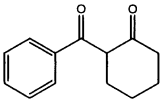
Table 1. Products obtained from the acylation of a series of Li enolates and their respective silyl enol ethers

Entry	Ketone	Acylating Reagent	Product	Yield %[a] (Li Enolate)	Conversion %[b,c] (Enol ether)
1	Acetophenone	Acetyl chloride	 1	89 [21]	-
2	Acetophenone	Acetyl cyanide	 2	92 [22]	97
3	Acetophenone	Benzoyl chloride	 3	56 [23]	-
4	Acetophenone	Benzoyl fluoride	 4	80	100
5	Acetophenone	Benzoyl cyanide	 5	93 [24]	98
6	Propiophenone	Benzoyl chloride	 6	95 [25]	-
7	Propiophenone	Benzoyl fluoride	 7	96	99
8	Cyclohexanone	Benzoyl chloride	 8	71 [26]	-
9	Cyclohexanone	Benzoyl fluoride	 9	70	100
10	Cyclohexanone	Benzoyl cyanide	 10	89	95

[a] Yields calculated based on the ketone, products generated from the lithium enolate.

[b] Conversions were calculated by GC-MS based on the amount of product with respect to the residual silyl enol ether.

[c] No results are reported for the acylation of silyl enol ethers using acyl chlorides as no reactions were observed.

C-acylation was observed in either reaction. Subsequent reactions of the Li enolate of acetophenone with acetyl cyanide and benzoyl cyanide however, resulted in the formation of the *C*-acylated products, benzoyl acetone **2**[22] and dibenzoylmethane **5**,[24] respectively. Again no contamination occurred from competing *O*-acylation (**1** and **3**).[23]

Upon treatment of the silyl enol ether of acetophenone with acetyl chloride and benzoyl chloride, no reactions were observed. This phenomenon was also noted by Olofson et al. whereby the use of chloroformates in place of fluoroformates impeded the synthesis of enol carbonates from silyl enol ethers.[27] The acyl chlorides were therefore replaced by their respective acyl fluoride and again, *O*-acylation was observed **4**. Treatment of the silyl enol ether of acetophenone with benzoyl cyanide resulted in *C*-acylation and the preparation of dibenzoylmethane **5**.[24] As Table 1 illustrates, the acylation of propiophenone[25] (**6** and **7**) and cyclohexanone[26] (**8**, **9** and **10**) via both the Li enolates and their respective silyl enol ethers resulted in the formation of the *C*-acylated product regardless of the acylating reagent used.

The regioselectivity of both the acylations of Li enolates and silyl enol ethers was found to be dependent upon the type of ketone used i.e. α-substituted ketones gave *C*-acylated products and non α-substituted resulted in *O*-acylation with acyl halides and *C*-acylation with acyl cyanides. In all cases, the products were found to be 100% *C*- or *O*-acylated, no mixtures were observed. In comparison to the use of acyl halides, the treatment of a Li enolate with an acyl cyanide showed an increase in yield. An increase in conversion was also observed when using the silyl enol ether approach, compared to the direct acylation of the Li enolate.

In conclusion, the use of silyl enol ethers is advantageous as it removes the effect of a metal counterion along with the observed reactions between aminated bases and acylating reagents. The procedure provides a simple, room temperature, route to the formation of uncontaminated 1,3-diketones or *O*-acylated products in high yields.

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17. *Example of a typical Li enolate procedure*: cyclohexanone (1.00 g, 10.20 mmol) was added dropwise to a stirred solution of lithium bis(trimethylsilyl)amide (LiHMDS) (10.20 ml, 1.0 M, 10.20 mmol) in THF (100 ml) over a period of 30 min. The resulting solution was stirred for a further 15 min prior to the addition of benzoyl fluoride (1.11 ml, 10.20 mmol) in THF (10 ml). The reaction mixture was stirred for 15 min and subsequently extracted using ethyl acetate (3×50 ml). The combined organic solvents were dried over magnesium sulfate and concentrated in vacuo. Purification was achieved using silica gel chromatography. Elution with 10% ethyl acetate in hexane yielded 2-benzoylcyclohexanone (1.44 g, 70%).
18. *Example of a typical silyl enol ether preparation*: A solution of cyclohexanone (0.10 g, 1.02 mmol) in anhydrous THF (10 ml) was added dropwise to a stirred solution of LiHMDS (1.02 ml, 1.0 M, 1.02 mmol) over a period of 30 min. The solution was then stirred for a further 15 min prior to the addition of chlorotrimethylsilane (0.13 ml, 1.20 mmol). The reaction mixture was concentrated in vacuo and the resulting residue dissolved in DCM (50 ml). The inorganics were removed by filtration and the resulting solution concentrated in vacuo to yield the silyl enol ether of cyclohexanone (0.16 g, 93%).
19. *Example of a typical acylation using a silyl enol ether*: The silyl enol ether of cyclohexanone (0.10 g, 0.59 mmol) was added dropwise to a stirred solution of *anhydrous* TBAF (0.015 g, 0.059 mmol) and benzoyl fluoride (0.06 ml, 0.59 mmol) in anhydrous THF (10 ml). The reaction mixture was extracted into ethyl acetate (3×50 ml) and the combined organic solvents dried over magnesium sulfate. Purification was achieved using silica gel chromatography. Elution with 10% ethyl actate in hexane gave 2-benzoyl cyclohexanone (100% conversion, calculated by GC-MS, with respect to residual silyl enol ether).

20. *Anhydrous* tetrabutylammonium fluoride was prepared from TBAF·$3H_2O$, purchased from Aldrich. The TBAF·$3H_2O$ was dried over phosphorous pentoxide under vacuum (10 mm Hg) for 48 h to afford a gelataneous solid. The use of TBAF·$3H_2O$ proved unsuccessful as a catalytic desilylation agent as the added moisture resulted in the protonation of the enolate, converting it back to the corresponding ketone.
21. Compound **1**: δ_H (400 MHz, $CDCl_3$/TMS) 2.24 (3H, s, CH_3), 4.87 (1H, d, *J* 2.2, C*H*H), 5.33 (1H, d, *J* 2.2, CH*H*), 7.29 (2H, m, Ar) and 7.33 (3H, m, Ar); *m*/*z* (EI) 163 (M^++1, 26%), 162 (65), 161 (100) and 105 (50).
22. Compound **2**: δ_H (400 MHz, $CDCl_3$/TMS) 2.19 (3H, s, CH_3), 6.17 (2H, s, CH_2), 7.43 (3H, m, Ar) and 7.86 (2H, m, Ar); δ_C (100 MHz, $CDCl_3$/TMS) 25.9 (CH_3), 96.8 (CH_2), 125.6 (CH), 128.7 (CH), 132.4 (CH), 134.9 (C), 183.4 (CO) and 194.0 (CO); *m*/*z* (EI) 163 (M^++1, 100%), 162 (30), 161 (35), 105 (45) and 77 (10).
23. Compound **3**: δ_H (400 MHz, $CDCl_3$/TMS) 5.16 (1H, d, *J* 2.3, C*H*H), 5.59 (1H, d, *J* 2.3, CH*H*), 7.35 (3H, m, Ar) and 7.95 (7H, m, Ar); δ_C (100 MHz, $CDCl_3$/TMS) 102.4 (CH_2), 125.0 (CH), 128.7 (CH), 128.8 (CH), 130.2 (CH), 133.7 (CH), 134.4 (C) and 134.7 (C); *m*/*z* (EI) 225 (M^++1, 5%), 224 (20), 105 (100) and 77 (20).
24. Compound **5**: δ_H (400 MHz, $CDCl_3$/TMS) 6.84 (2H, s, CH_2), 7.51 (6H, m, Ar) and 7.98 (4H, m, Ar); δ_C (100 MHz, $CDCl_3$/TMS) 93.3 (CH_2), 127.3 (CH), 128.8 (CH), 132.6 (CH), 135.6 (C) and 185.9 (CO); *m*/*z* (EI) 225 (M^++1, 25%), 224 (50), 223 (75), 105 (100) and 77 (75).
25. Compound **6**: δ_H (400 MHz, $CDCl_3$/TMS) 1.59 (1H, d, *J* 7.0, CH_3), 5.28 (3H, q, *J* 7.0, CH), 7.96 (6H, m, Ar) and 7.45 (4H, m, Ar); δ_C (100 MHz, $CDCl_3$/TMS) 14.5 (CH_3), 51.1 (CH_2), 128.6 (CH), 129.0 (CH), 130.0 (CH), 133.6 (C) and 197.3 (CO); *m*/*z* (EI) 239 (M^++1, 2%), 238 (10) and 105 (100).
26. Compound **8**: δ_H (400 MHz, $CDCl_3$/TMS) 1.74 (2H, m, CH_2), 1.98 (2H, m, CH_2), 2.28 (2H, m, CH_2), 2.54 (2H, m, CH_2), 4.38 (1H, m, CH), 7.44 (2H, m, Ar), 7.54 (1H, m, Ar) and 7.89 (2H, m, Ar); δ_C (100 MHz, $CDCl_3$/TMS) 23.2 (CH_2), 23.5 (CH_2), 27.4 (CH_2), 30.1 (CH_2), 58.9 (CH), 128.6 (CH), 128.7 (CH), 133.3 (CH), 136.6 (C), 197.7 (CO) and 208.7 (CO); *m*/*z* (EI) 203 (M^++1, 15%), 202 (30), 201 (28), 105 (100) and 77 (55).
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