A Synthesis of α,α-Disubstituted Aryl-β-ketoesters

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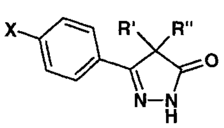
Abstract: A generally applicable synthesis of α,α-disubstituted β-ketoesters involving reaction of a substituted benzoyl chloride with methyl trimethylsilyl ketene acetal is described. Addition of boron trifluoride etherate is essential when the benzoyl chloride is not substituted with a strongly electron withdrawing residue. The majority of experiments were conducted with the dimethylketene acetal but the process is equally applicable to the cyclohexaneketene acetal **5**.

α,α-Disubstituted-β-ketoesters are frequently used as intermediates in the synthesis of a range of heterocyclic systems. For example, the pyrazol-3-ones, **1**, are readily available from the β-ketoesters, **2**, and have been examined as potential agents for the treatment of congestive heart failure.[1] However, there are very few practical methods for the preparation of pure α,α-dialkylated-β-ketoesters on a multigram scale. This parsity of routes is particularly evident when the aryl ring features an eletron withdrawing substituent.



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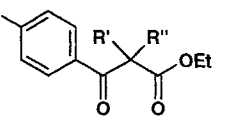

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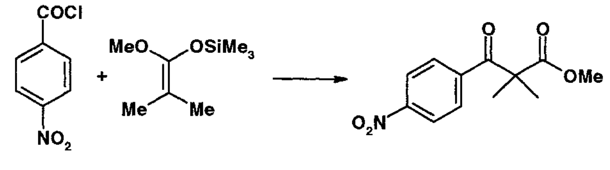
The most common approach to α,α-dialkyl-β-ketoesters is by direct alkylation[2], and development of new procedures continues to attract attention[3,4,5], including those that lead to the construction of asymmetrically dialkylated chiral materials. Nevertheless, this approach can suffer from the production of O-alkylated or mono-alkylated products which are difficult to remove from the desired product. Construction of the Ar(O=)C-C bond by acylation of ester enolates or their equivalents is an alternative strategy which avoids these difficulties. Useful results have been obtained by reaction of 4-substituted benzoyl chlorides and the lithium salt of t-butyl butyrate, however, the yields are low when the aryl substituent is electron withdrawing[6]. Use of Reformatsky-type reagents has also been reported for several benzoyl chlorides though not for cases where the aryl substituent is electron-withdrawing[7].

It has been reported that ethyl t-butyldimethylsilylketene acetals possessing one or no α-substituents react with acid chlorides in the presence of triethylamine to give the silyl enol ether derivatives of the corresponding β-ketoesters. The α,α-dimethyl compounds are expected to be inert under these conditions[8]. In contrast, a recent comment by Yang and Wnek[9] indicated that 4-nitrobenzoyl chloride reacts with methyl trimethylsilyl dimethylketene acetal (MTDA) **3** to give the α,α-dimethyl-β-ketoester **4** in high yield (Scheme 1). This prompted us to investigate the general applicability of this reaction. In this paper we describe our initial results on the key role that substituents play in this reaction. The use of this methodology has provided a major breakthrough for our synthetic strategies and allowed us to prepare α,α-dialkylated-β-ketoesters unobtainable by other methods.

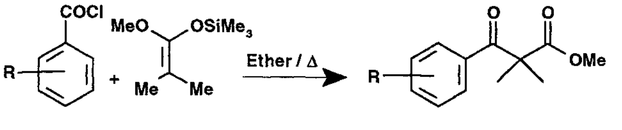


3 **4**

Scheme 1

In cases where the benzoyl chloride was substituted with a strongly electron withdrawing substituent in either the *meta* or *para* position, refluxing with one equivalent of MTDA in dry ether in an inert atmosphere for 24 hours gave good yields of the corresponding α,α-disubstituted β-ketoester (entries 1-4 table 1). In the cases where the substituent was strongly electron donating (NMe_2, OMe) or slightly electron donating (Me, Cl) one equivalent of boron trifluoride etherate ($BF_3.Et_2O$) was required. A likely reaction mechanism for this reaction involves attack by the ketene acetal on the acyl chloride and thus the role of the $BF_3.Et_2O$ could be to complex with the carbonyl of the acyl chloride in order to activate it towards nucleophilic attack. Even in the cases of methoxy- and dimethylamino-substituted benzoyl chlorides, it may be that the $BF_3.Et_2O$ is complexing to the acyl chloride as demonstrated by Greenvald and Rabinovitz[10] for p-anisaldehyde. In the case of the *ortho*-substituted benzoyl chlorides, increasing the quantity

Table 1



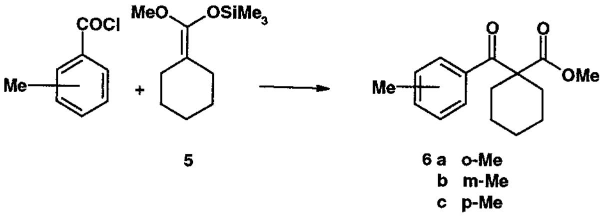
No	Substituent	Yield (%)	Yield (%) A	Yield (%) B
1	m-NO_2	78	-	-
2	p-NO_2	75	-	-
3	m-CN	67	-	-
4	p-CN	63	-	-
5	o-CF_3	0	19	-
6	m-CF_3	76	61	-
7	p-CF_3	8	41	-
8	p-CHO	7	9	-
9	o-F	0	1	30
10	m-F	18	38	43
11	p-F	0	13	46
12	o-C1	1	26	46
13	m-C1	23	78	56
14	p-C1	0	32	53
15	H	0	64	50
16	o-Me	0	35	53
17	m-Me	0	54	51
18	p-Me	0	46	54
19	m-OCF_3	15	54	-
20	p-OCF_3	6	41	-
21	m-OCH_3	0	63	-
22	p-OCH_3	0	83	-
23	p-NMe_2	0	70	-

A with one equivalent of $BF_3.Et_2O$
B with three equivalents of $BF_3.Et_2O$

of $BF_3.Et_2O$ to three equivalents improved the yields. In general, however, the addition of two further equivalents of $BF_3.Et_2O$ had only a marginal effect. The reaction conditions are not tolerated by an aldehyde substituent (entry 8) which presumably reacts with the ketene acetal to give an aldol-type product.

All products were fully characterised by ^1H, ^{13}C NMR and satisfactory micro-analysis. Yields are for isolated material but are unoptimised.

The scope of this reaction, for example to allow the introduction of alternative α,α-substituents, has only been investigated to a limited extent. However, the reactions of the cyclohexaneketene acetal **5** with each of the three isomeric methylbenzoyl chlorides, in the presence of three equivalents of boron trifluoride, produced the ketoesters **6a-c** in moderate yield, typically 40-50%. These results are encouraging and further work is underway to extend the reaction and to optimise the experimental proceedure.



In summary, treatment of an aroyl chloride with a methyl trimethylsilylketene acetal offers a very promising, straightforward and generally applicable route to α,α-disubstituted β-ketoesters. It is likely that this procedure could be extended to include unsymmetrically substituted ketene acetals, as well as cyclic systems and ketene acetals that feature additional heteroatoms.

General procedure

MTDA (10 mmol) was added to a solution of the benzoyl chloride (10 mmol) in dry ether (26 ml) under nitrogen, $BF_3.Et_2O$ (10 or 30 mmol) was added if required, and the mixture refluxed for 24 h. The reaction mixture was washed with aqueous sodium hydroxide (1M), water and brine and filtered through $MgSO_4$. Flash chromatography (hexane/ethyl acetate, typically 4:1) gave the pure product.

Avoidance of the alkaline wash gave enhanced yields of products in some cases (e.g. the 2-F derivative), but often led to more difficult chromatographic separations, if excess acyl chloride was not fully hydrolysed.

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