Hexamethylenetetramine-Mediated Transesterification of β-Keto Esters

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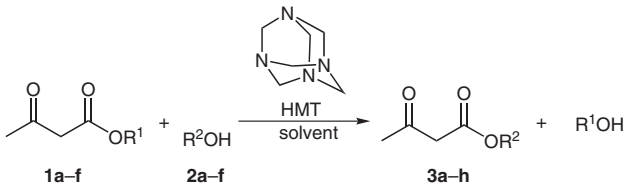
Abstract: Treatment of methyl or ethyl β-keto esters with primary, secondary, or tertiary alcohols in the presence of a catalytic amount of hexamethylenetetramine results in good to high yields of the corresponding esters.

Key words: transesterification, hexamethylenetetramine, β-keto esters

The transesterification of β-keto esters has been recognized as one of the most important processes in producing other β-keto esters, having wide application in academic and industrial research.[1–4] Many useful methods for transesterification of β-keto esters have been reported in the literature.[3–12] Some of the recently developed methods involve the use of *N*,*N*-diethylaminopropylated silica gel (NDEAP),[3] natural clays,[4] zinc dust,[5] *N*-bromosuccinimide,[6] zeolites,[7] iodine,[8] 1,8-diazabicyclo[5.4.0]undec-7-ene,[9] 4-(*N*,*N*-dimethylamino)pyridine,[10] tetrabutyl distannoxanes,[11] and Amberlyst-15.[12] These protocols are normally efficient; however, most of these methods suffer from one or more of the following disadvantages: long reaction times, and the use of toxic and expensive reagents, and in relatively large amounts. From the environmental as well as economical points of view, new efficient methods for transesterification are potentially very useful.

We wish to report that hexamethylenetetramine (HMT) acts as an efficient catalyst to effect transesterification of β-keto esters (Scheme 1).



Scheme 1

Hexamethylenetetramine is a very inexpensive, nonhygroscopic, and stable reagent of low toxicity.[13,14] It can be prepared easily, by allowing a mixture of formalin and concentrated ammonia solution to evaporate.[13] Hexamethylenetetramine is soluble in water, chloroform, ethanol, and some other organic solvents,[14] and is employed in medicine under the name urotropine as a urinary antiseptic.[13] This versatile synthetic reagent has been used in the preparation of primary amines and N-heterocycles[14] and as an efficient catalyst precursor for the microwave-assisted Knoevenagel reaction.[15] Recently, we have demonstrated that hexamethylenetetramine can be used as a convenient catalyst in the Baylis–Hillman reaction.[16]

As a model reaction, the transesterification of methyl acetoacetate (**1a**) with (–)-menthol (**2a**) was studied (Table 1, entries 1–4: methods A, B, or C). The reaction between **1a** (3 mmol) and (–)-menthol (**2a**; 1 mmol) in the presence of catalytic amounts of hexamethylenetetramine (0.3 mmol) in toluene solution at reflux (24 h) gave menthyl acetoacetate (**3a**) in 73% yield (method A, entry 1). When the transesterification was carried out in refluxing toluene with a Dean–Stark trap, the yield could be improved to 86% (method B, entry 2), and azeotropic transesterification in cyclohexane[10b] instead of toluene gave a yield of 93% (method C, entry 3). Under the same conditions, but in the absence of hexamethylenetetramine, the yield of this reaction decreased to 53% (entry 4).

This procedure is quite general, as a wide range of structurally varied β-keto esters such as open-chain, cyclic, and aromatic esters underwent transesterification with various alcohols (Table 1). The reaction with *tert*-butyl alcohol, which is often problematic with other protocols, is also realized with this reagent, but in moderate yields (49–60%; toluene/Dean–Stark) (Table 1, entries 10, 14). In this case, an excess of *tert*-butyl alcohol is necessary to compensate for its volatility (method D). We have also investigated the preparation of *tert*-butyl acetoacetate (**3e**) under the same reaction conditions described above (method D), but without the catalyst[17] (entry 15). Although the reaction can be accomplished without hexamethylenetetramine, only a low yield of **3e** (10%) was obtained. Transesterification between an α-substituted acetoacetate **1d** and *tert*-butyl alcohol also led to a low yield of product (entry 16); this can be attributed to the bulkiness of the substrate and hexamethylenetetramine. However, no efforts were made to optimize the yield of product **3g**. The transesterification of α,α-disubstituted β-keto ester **1e** (entries 17, 18) resulted in complete recovery of the substrate; this suggests that this reaction proceeds via a ketene intermediate.[3]

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Table 1 HMT-Mediated Transesterification of β-Keto Esters

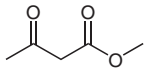
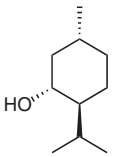
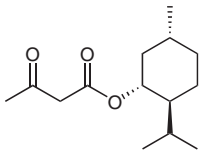
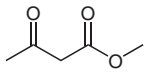
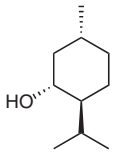
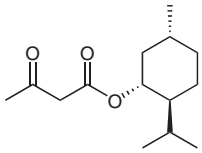
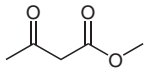
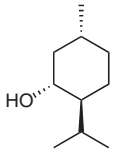
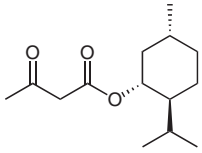
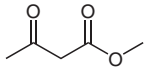
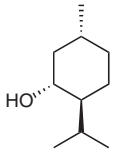
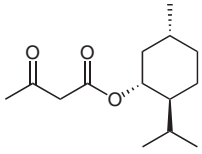
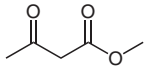
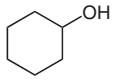
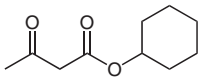
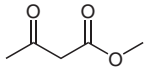
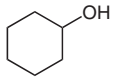
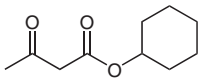
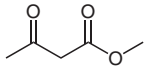
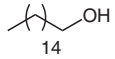
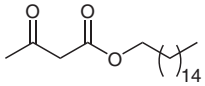
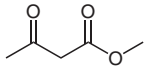
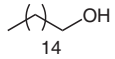
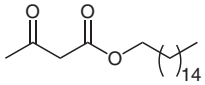
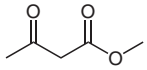
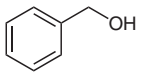
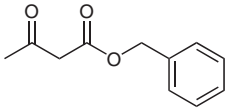
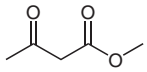
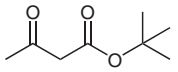
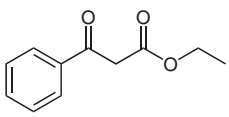
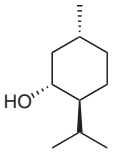
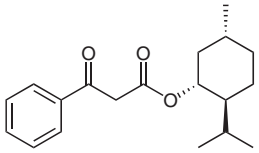
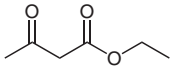
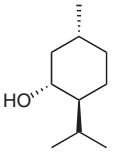
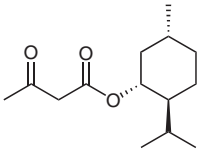
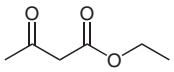
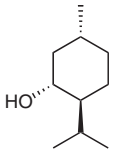
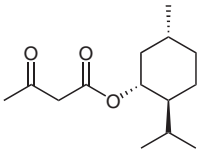
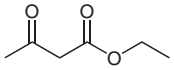
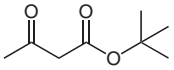
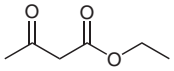
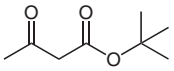
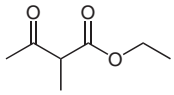
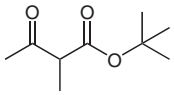
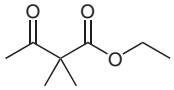
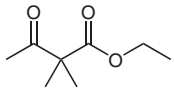
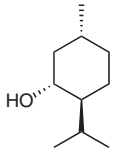
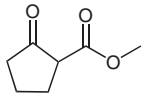
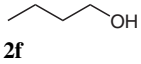
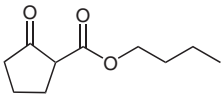
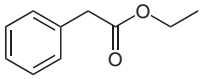
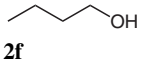
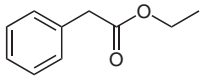
Entry	Ester **1**	Alcohol **2**	Product **3**[a]	Method[b]	Yield[c] (%)
1	 **1a**	 **2a**	 **3a**	A	73
2	 **1a**	 **2a**	 **3a**	B	86
3	 **1a**	 **2a**	 **3a**	C	93
4	 **1a**	 **2a**	 **3a**	C[d]	53
5	 **1a**	 **2b**	 **3b**	A	70
6	 **1a**	 **2b**	 **3b**	C	85
7	 **1a**	 **2c**	 **3c**	A	78
8	 **1a**	 **2c**	 **3c**	C	84
9	 **1a**	 **2d**	 **3d**	C	92
10	 **1a**	 **2e**	 **3e**	D	60
11	 **1b**	 **2a**	 **3f**	C[e]	67

Table 1 HMT-Mediated Transesterification of β-Keto Esters (continued)

Entry	Ester **1**	Alcohol **2**	Product **3**[a]	Method[b]	Yield[c] (%)
12	 **1c**	 **2a**	 **3a**	B	75
13	 **1c**	 **2a**	 **3a**	C	89
14	 **1c**	 **2e**	 **3e**	D	49
15	 **1c**	 **2e**	 **3e**	D[d]	10
16	 **1d**	 **2e**	 **3g**	D	8
17	 **1e**	 **2e**	no reaction	D	–
18	 **1e**	 **2a**	no reaction	C	–
19	 **1f**	 **2f**	 **3h**	C[e]	63
20	 **1g**	 **2f**	no reaction	B	–
21	 **1g**	 **2g**	no reaction	B	–
22	Trimyristin **1h**	MeOH **2h**	no reaction	B	–

[a] Products were characterized by spectral analysis.
[b] Reagents and conditions: Method A: ester **1** (3 equiv), alcohol **2** (1 equiv), HMT (0.3 equiv), toluene, reflux; Method B: ester **1** (3 equiv), alcohol **2** (1 equiv), HMT (0.3 equiv), toluene, reflux, Dean–Stark trap; Method C: ester **1** (3 equiv), alcohol **2** (1 equiv), HMT (0.3 equiv), cyclohexane, reflux, Dean–Stark trap; Method D: ester **1** (3 equiv), alcohol **2** (excess), HMT (0.3 equiv), toluene, reflux, Dean–Stark trap.
[c] Yield of analytically pure sample.
[d] Without catalysis (absence of HMT).
[e] Ester **1** (1 equiv), alcohol **2** (1.2 equiv).

The yields of products **3f**[7a] and **3h**[5] (entries 11, 19), obtained from transesterification of β-keto esters **1b** and **1f** (1 equiv) with the respective alcohols **2a** and **2f** (1.2 equiv) were moderate. This may be attributed to the bulkiness of the substrates.

It is important to note that the reaction appears to be specific only for the transesterification of β-keto esters, as others esters such as ethyl phenylacetate (**1g**) (Table 1, entries 20, 21) and the triglyceride trimyristin **1h** (entry 22) failed to undergo the reaction.

In conclusion, we have demonstrated that hexamethylenetetramine is an efficient and inexpensive catalyst to effect transesterification of methyl or ethyl β-keto esters (unsubstituted and monosubstituted substrates).

(–)-Menthyl 3-Oxobutanoate (3a);[8] Typical Procedure (Method C)

A mixture of methyl acetoacetate (**1a**; 696 mg, 6 mmol), (–)-menthol (**2a**; 312 mg, 2 mmol), and HMT (84 mg, 0.6 mmol) in cyclohexane (13 mL) was heated for 24 h in a flask connected to a Dean–Stark trap. The mixture was filtered and the filtrate was washed with 5% aq HCl soln (2 × 8 mL) and dried (Na_2SO_4). Evaporation of the organic phase was followed by purification by flash chromatography (silica gel, 230–400 mesh, 13 × 1.8 cm, EtOAc–hexane, 1:9).

Yield: 446 mg (93%); oil; $[\alpha]_D^{20}$ –69.00 (*c* 12, benzene).[8]

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