

Note

Tetraethylammonium superoxide induced Michael addition of active methylene compounds to chalcones

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Michael addition of active methylene compounds to chalcones using *in-situ* generated tetraethylammonium superoxide results in the formation of Michael adducts in 69-84% yield under mild reaction conditions, at room temperature.

Keywords: Michael addition, superoxide, chalcones, active methylene compounds

Michael addition reactions of active methylene compounds to α,β -unsaturated ketones are of great synthetic interest for carbon-carbon bond formation¹. The versatility of this reaction has numerous applications in the elegant synthesis of useful products². Traditionally, these reactions are catalyzed by strong bases such as alkali metal alkoxides. Several undesirable side reactions are caused by these strongly basic catalysts including rearrangements, secondary condensation, isomerizations, polymerizations, bis additions, retrogressions and transesterifications³. These undesirable side reactions decrease the yield and make the purification of products very difficult¹. In the last few years, various catalysts such as phase transfer catalysts⁴, metal (Co, Zn, Ni) (II) complexes⁵, alumina⁶, SnCl_4 (Ref. 7), CsF (Ref. 8), $\text{Bu}_2\text{Sn}(\text{OTf})_2$ (Ref. 9), $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (Ref. 9), BiCl_3 or CdI_2 (Ref. 10), $\text{EuCl}_3 \cdot 6\text{H}_2\text{O}$ (Ref. 11), $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (Ref. 12) and $\text{K}_2\text{CO}_3/\text{MW}$ ¹³ have been employed.

As a part of the ongoing research programme on superoxide chemistry¹⁴, it is wished to report herein

the results on the reaction of *in-situ* generated tetraethylammonium superoxide with ethyl acetoacetate or diethyl malonate in the presence of chalcones (**Scheme I**).

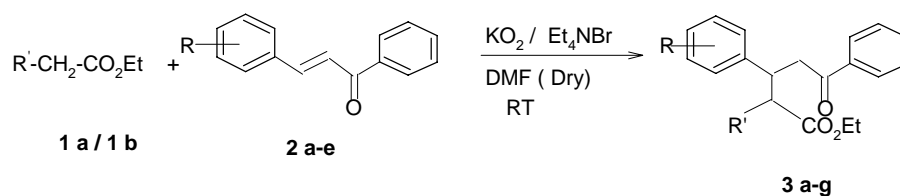
In the course of reaction, tetraethylammonium superoxide was generated *in-situ* by the phase transfer reaction of KO_2 and Et_4NBr in dry DMF at RT and was subsequently allowed to react with Michael donors **1a/1b** and acceptors **2a-e**. The results are given in **Table I**. As an outcome, Michael acceptor chalcones **2a-e** readily reacted with ethyl acetoacetate **1a** or diethyl malonate **1b** to give Michael addition products **3a-g** in reasonably good to excellent yields (69-84%).

A molar ratio of 1:1:0.5 for substrate **2**: KO_2 : Et_4NBr was employed for achieving the reaction. Each reaction was monitored by TLC for its completion. The products were fully identified by their physical and spectral data, which are in full agreement with the values described in literature^{3e,13}.

In conclusion, tetraethylammonium superoxide promoted addition of ethyl acetoacetate or diethyl malonate to chalcones offers an efficient and attractive way to carbon-carbon bond formation and proceeds under significantly mild conditions at RT.

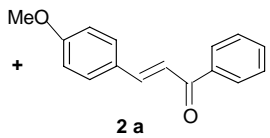
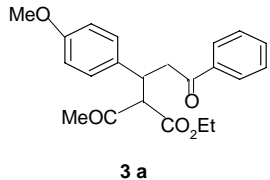
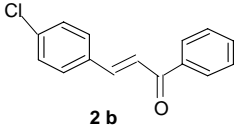
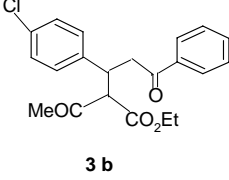
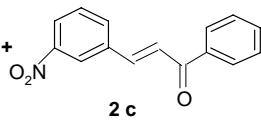
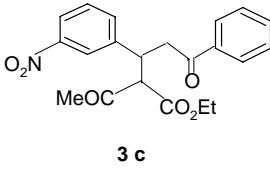
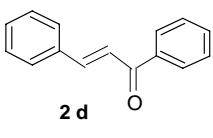
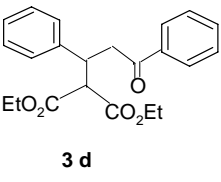
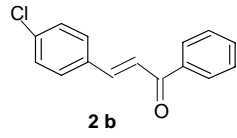
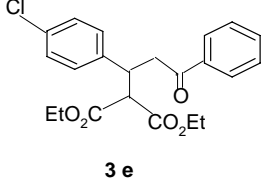
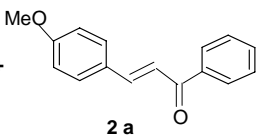
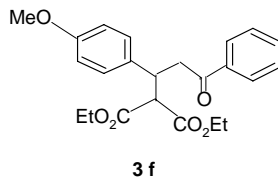
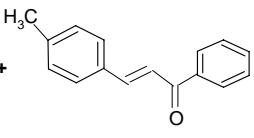
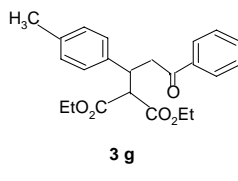
Experimental Section

Potassium superoxide and tetraethylammonium bromide were procured from E. Merck, and were used as received. Dry DMF of Aldrich, was stored over molecular sieves (4Å) prior to use. Ethyl acetoacetate **1a** and diethyl malonate **1b** were purchased from Aldrich, whereas chalcones were prepared according to literature procedure¹⁵. Melting points were measured in open capillaries and are uncorrected. IR spectra were recorded on a JASCO FT/IR-5300 spectrophotometer. NMR spectra were run on a JEOL AL300 FT-NMR and chemical shift are expressed as δ (ppm), using TMS as internal reference.



Scheme I

Table I — Reaction of $\text{KO}_2/\text{Et}_4\text{NBr}$ with ethyl acetoacetate **1a** or diethyl malonate **1b** in the presence of chalcones **2a-e**

| Reactants | | Product | Yield (%) |
|---|---|--|-----------|
| $\text{MeCOCH}_2\text{CO}_2\text{Et}$ 1 a |  2 a |  3 a | 76 |
| $\text{MeCOCH}_2\text{CO}_2\text{Et}$ 1 a |  2 b |  3 b | 84 |
| $\text{MeCOCH}_2\text{CO}_2\text{Et}$ 1 a |  2 c |  3 c | 69 |
| $\text{CH}_2(\text{CO}_2\text{Et})_2$ 1 b |  2 d |  3 d | 73 |
| $\text{CH}_2(\text{CO}_2\text{Et})_2$ 1 b |  2 b |  3 e | 80 |
| $\text{CH}_2(\text{CO}_2\text{Et})_2$ 1 b |  2 a |  3 f | 75 |
| $\text{CH}_2(\text{CO}_2\text{Et})_2$ 1 b |  2 e |  3 g | 76 |

General procedure for the reaction of *in-situ* generated tetraethylammonium superoxide with ethyl acetoacetate or diethyl malonate in the presence of chalcones

Potassium superoxide (0.28 g; 0.004 mole) and tetraethylammonium bromide (0.42 g; 0.002 mole) were weighed under nitrogen atmosphere using an atmosbag and were transferred into a three necked round bottom flask fitted with a dropping funnel, magnetic stirrer, nitrogen inlet and a Leibig condenser protected by calcium chloride drying tube. Dry dimethylformamide (30 mL) was added to it and the mixture was agitated magnetically for 15 min to facilitate the formation of tetraethylammonium superoxide. To the stirred reaction mixture, were added ethyl acetoacetate or diethyl malonate (0.004 mole) and chalcone (0.004 mole) successively. Nitrogen was bubbled continuously and reaction mixture was stirring magnetically for 3-6 hr at RT until the starting material was consumed as indicated by TLC. After the reaction was over, mixture was treated with brine solution (20 mL) followed by saturated sodium hydrogen carbonate solution (20 mL) and then extracted with diethyl ether (3 × 20 mL). The combined organic phase was dried over Na₂SO₄ (anhyd.), filtered and evaporated to give the crude addition product **3**, which was purified by column chromatography using silica gel (60-120 mesh) as adsorbent and ethyl acetate/*n*-hexane as the eluent.

3a: IR (KBr): 1748, 1725, 1687, 1276 cm⁻¹; ¹H NMR (CDCl₃): δ 1.2 (t, 3H), 2.4 (s, 3H), 3.5 (dd, 1H), 3.8-3.9 (m, 2H), 4.0 (s, 3H), 4.1 (q, 2H), 4.2 (m, 1H), 7.0-7.9 (m, 9H).

3b: IR (KBr): 1754, 1735, 1680 cm⁻¹; ¹H NMR (CDCl₃): δ 1.1 (t, 3H), 2.4 (s, 3H), 3.6 (dd, 1H), 3.7 (d, 1H), 3.9 (dd, 1H), 4.0 (q, 2H), 4.2 (m, 1H), 7.2-7.9 (m, 9H).

3c: ¹H NMR (CDCl₃): δ 1.2 (t, 3H), 2.5 (s, 3H), 3.7 (m, 2H), 4.0-4.2 (m, 4H), 7.1-8.3 (m, 9H).

3d: IR (KBr): 1720, 1680 cm⁻¹; ¹H NMR (CDCl₃): δ 1.0 (t, 3H), 1.3 (t, 3H), 3.3-3.6 (m, 2H), 3.8 (d, 1H), 3.9-4.0 (m, 1H), 4.1-4.3 (m, 4H), 7.1-7.8 (m, 10H).

3e: IR (KBr): 1730, 1687 cm⁻¹; ¹H NMR (CDCl₃): δ 1.0 (t, 3H), 1.2 (t, 3H), 3.4-3.5 (m, 2H), 3.8 (d, 1H), 4.0 (dd, 2H), 4.2 (m, 3H), 7.2-7.9 (m, 9H).

3f: IR (KBr): 1724, 1678 cm⁻¹; ¹H NMR (CDCl₃): δ 1.1 (t, 3H), 1.3 (t, 3H), 3.4-3.5 (m, 2H), 3.7 (s, 3H), 3.8 (d, 1H), 4.0 (m, 2H), 4.1-4.2 (m, 3H), 6.9-8.0 (m, 9H).

3g: IR (KBr): 1727, 1682 cm⁻¹; ¹H NMR (CDCl₃): δ 1.0 (t, 3H), 1.3 (t, 3H), 2.3 (s, 3H), 3.4-3.6 (m, 2H), 3.8 (d, 1H), 4.0 (m, 2H), 4.1-4.2 (m, 3H), 7.0-7.9 (m, 9H).

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