

Short Note

# Methyl 3,3-Bis[4-(dimethylamino)phenyl]-2,2-dimethylpropanoate

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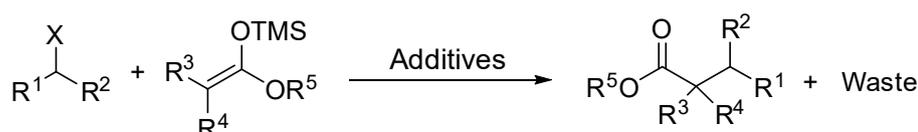
**Abstract:** The synthesis of methyl 3,3-bis[4-(dimethylamino)phenyl]-2,2-dimethylpropanoate is achieved by means of the alkylation of methyl isobutyrate silyl enol ether with bis[4-(dimethylamino)phenyl]methanol, facilitated by using 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) as a solvent and reaction promoter. The reaction proceeds smoothly to produce the mentioned compound in a good yield via a metal and additive-free procedure. The corresponding ester is fully characterized.

**Keywords:** HFIP; ketene silyl acetals; alkylation;  $S_N1$ ; alcohol

## 1. Introduction

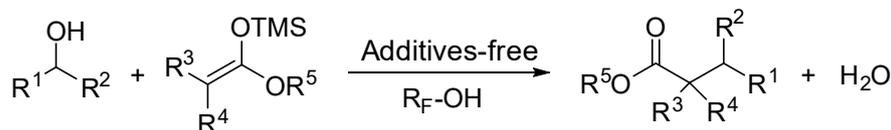
The alkylation reaction of ketene silyl acetals with different electrophiles is a well-established methodology in organic synthesis. However, this reaction normally requires the use of an alcohol derivative, such as tosylates, carbonates, acetates, or halides, as a substrate. Additionally, sometimes, a fluoride source and/or Brønsted or Lewis acid are also necessary to activate the corresponding nucleophile and/or electrophile, respectively, (Scheme 1). Thus, the overall process generates a stoichiometric amount of waste. Therefore, a much more attractive strategy from practical and environmental points of view would be the direct use of alcohols to carry out this transformation since they are readily available compounds from raw materials and only generate water as a by-product [1].

### Well established methodology (Eq. a)



X = OTs, OC(O)R, OC(O)OR, Hal....

### Less common methodology (Eq. b)



**Scheme 1.** Alkylation reaction of ketene silyl acetals.

On the other hand, to continue our studies on the use of fluorinated alcohols as solvents and promoters of chemical transformations [2–6], we used fluoroalkyl alcohols to accomplish the above-mentioned transformation (Scheme 1). This idea arose not only because of the unique chemical and physical properties (such as a high hydrogen bond donor ability, low nucleophilicity, high polarity and ionizing power values and slight Brønsted acidity) of fluorinated alcohols [7–9], but also because they have both shown to



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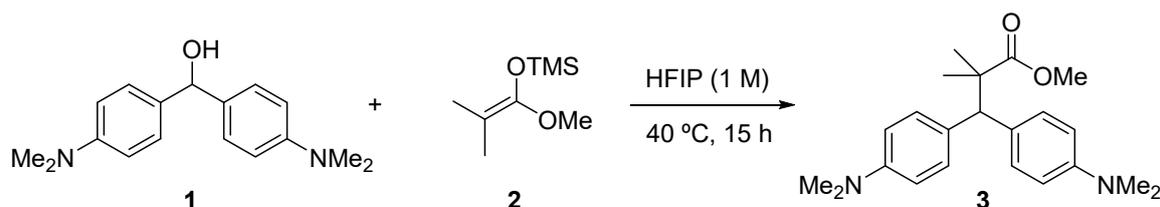


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promote nucleophilic substitution reactions onto the so-called activated alcohols (such as benzylic and allylic alcohols) [10] and activate silicon-based nucleophiles [11].

## 2. Results

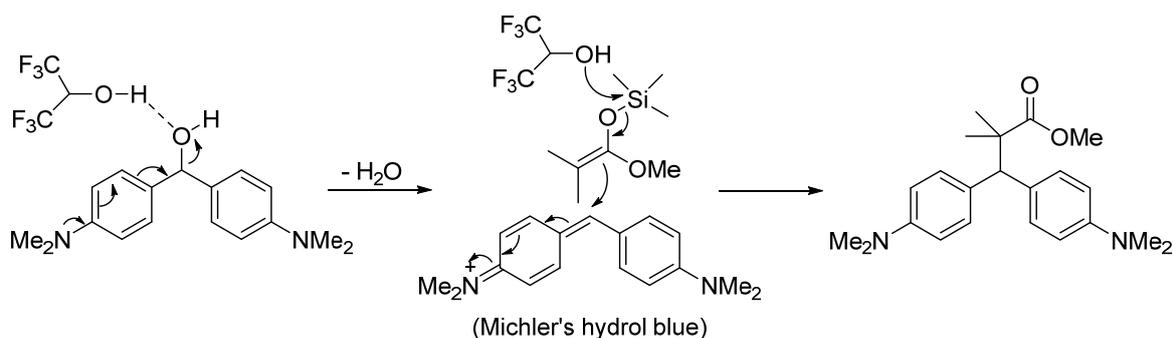
The synthesis of the mentioned ester was accomplished following a previous methodology developed by our group [11]. Thus, benzhydrol **1** was allowed to react with silyl enol ether **2** at 40 °C using 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) as a solvent and reaction promoter (Scheme 2). After 15 h, the solvent was evaporated, and after purification, compound **3** was obtained in a 62% yield.



Scheme 2. Synthesis of ester **3**.

It is important to remark that other polar solvents, which are known to be substrates' activators via hydrogen bonding, such as H<sub>2</sub>O or MeOH, failed to have the desired effect in this reaction, and unaltered benzhydrol **1** or other non-desired products were observed. The corresponding ester **3** was observed via GC-MS, although in low conversion, only when 2, 2, 2-trifluoroethanol (TFE) was used.

Concerning the reaction mechanism (Scheme 3), an S<sub>N</sub>1-type process will seemingly occur. Firstly, the HFIP-mediated dehydroxylation of benzylic alcohol **1** will take place. This step is assumed from the fact that from as soon as HFIP was added to the reaction vessel containing compound **1**, a deep blue solution was observed, indicating the formation of the highly stable cation, known as Michler's hydrol blue [12]. Then, the attack by corresponding ketene silyl acetals, which can be also activated by means of HFIP, on this intermediate will render the corresponding ester **3**.



Scheme 3. Proposed reaction mechanism.

## 3. Materials and Methods

All reagents and solvents were purchased from commercial suppliers and used without further purification. NMR spectra were acquired with a Bruker AV-400 (Bruker Corporation, Karlsruhe, Germany) using CDCl<sub>3</sub> as a solvent. Low-resolution mass spectra (MS) were recorded in the electron impact mode (EI, 70 eV, He as carrier phase) using Agilent GC/MS 5973 Network Mass Selective Detector spectrometer apparatus equipped with an HP-5MS column (Agilent technologies, 30 m × 0.25 mm) and giving fragment ions in m/z, with relative intensities (%) in parentheses. High-resolution mass spectra (HRMS) were obtained using Agilent 7200 Quadrupole-Time of Flight apparatus (Q-TOF) (Agilent Technologies, Palo Alto, CA, USA); the form of ionization employed was electron impact (EI). IRs were recorded on a JASCO FT-IR 4100 LE Pike Miracle ATR (Jasco Analítica Spain, Madrid,

Spain), and only the most structurally relevant peaks are listed. Analytical TLC was performed on Merck silica gel plates, and the spots were visualized with UV light at 254 nm (Merck Millipore, Billerica, MA, USA). Flash chromatography was conducted using Merck silica gel 60 (0.040–0.063 mm).

#### General Procedure for the HFIP-Promoted Synthesis of Ester 3

In a capped tube, HFIP (250  $\mu$ L) was added in one portion onto a mixture of bis[4-(dimethylamino)phenyl]methanol **1** (0.25 mmol) and ketene silyl acetal **2** (0.625 mmol, 2.5 equiv.). The reaction was then stirred at 40  $^{\circ}$ C for 15 h. After this time, the solvent evaporated, and the crude material was directly purified via flash chromatography.

Methyl 3,3-bis[4-(dimethylamino)phenyl]-2,2-dimethylpropanoate (**3**):

Purple-blue sticky oil; purification via flash chromatography (hexane/EtOAc), 62% yield;  $R_f = 0.67$  (hexane/ethyl acetate 4/1); IR (ATR):  $\nu = 1724, 1612, 1516, 1346, 1265, 1234, 1130, \text{cm}^{-1}$ ;  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}} = 7.20$  (d,  $J = 8.5$  Hz, 4H), 6.71 (d,  $J = 8.5$  Hz, 4H), 4.26 (s, 1H), 3.55 (s, 3H), 2.93 (s, 12H), 1.28 (s, 6H) ppm;  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}} = 178.6, 148.5, 130.4, 130.0, 112.7, 57.4, 51.7, 46.9, 41.0, 24.3$  ppm; MS (EI):  $m/z$  354 ( $\text{M}^+$ , 3.6%), 254 (65), 253 (100), 237 (47), 165 (12), 126 (39), 118 (13); HRMS calcd for  $\text{C}_{22}\text{H}_{30}\text{N}_2\text{O}_2$ : 354.2307; found: 354.2285 (Supplementary Materials).

## 4. Conclusions

In conclusion, herein, we have described the synthesis of methyl 3,3-bis[4-(dimethylamino)phenyl]-2,2-dimethylpropanoate (**3**) in a good yield using a metal- and additive-free strategy by using 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) as a solvent and promoter in the reaction between methyl isobutyrate silyl enol ether (**2**) and bis[4-(dimethylamino)phenyl]methanol (**1**). The corresponding ester was obtained in a good yield under smooth reaction conditions. In addition, the implemented process possesses a high atom economy, generating water as a by-product.

**Supplementary Materials:** The following materials are available online:  $^1\text{H-NMR}$ ,  $^{13}\text{C-NMR}$ , IR, GC-MS, and HRMS of compound **3**.

**Author Contributions:** Conceptualization, A.B.; methodology, L.M.-G. and A.B.; investigation, L.M.-G.; data curation, L.M.-G. and A.B.; writing—original draft preparation, L.M.-G. and A.B.; writing—review and editing, A.B.; supervision, A.B.; funding acquisition, A.B. All authors have read and agreed to the published version of the manuscript.

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**Conflicts of Interest:** The authors declare no conflict of interest.

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