



Synthesis of functionalized triarylmethanes based on a 'FeCl₃-catalyzed benzylation/[3+3] cyclocondensation' strategy

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ABSTRACT

Functionalized triarylmethanes are prepared in two steps by FeCl₃-catalyzed benzylation of acetylacetone to give 3-(diarylmethyl)pentane-2,4-diones and subsequent formal [3+3] cyclization of the latter with 1,3-bis(trimethylsilyloxy)-1,3-dienes.

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Triarylmethanes are of considerable pharmacological relevance and occur in a number of natural products. Pharmacological activities include estrogen receptor binding affinity,^{1a} inhibition of hepatic cholesterol,^{1b} inhibition of aldose reductase 2,^{1c} antiproliferative activities,^{1d} antiviral and cytotoxic activity,^{1e} antifungal activity,^{1f} anti-HIV activity,^{1g,h} and CNS activity.¹ⁱ Naturally occurring triarylmethanes, containing a (1,1-diphenylmethyl)phenol substructure, include molsenone and a number of related molecules.² (1,1-Diphenylmethyl)salicylates and related structures have been reported to possess anti-HIV activity^{3a,1g} and antibacterial activity.^{3b}

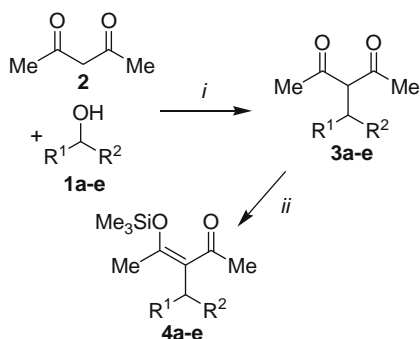
Well-known C–C coupling reactions, such as Friedel–Crafts alkylations, are used for the functionalization of arenes. In spite of the great synthetic utility of these methods, they have several drawbacks, such as drastic reaction conditions and the formation of regioisomeric mixtures or isomerization products. To address these problems, Beller and coworkers developed novel FeCl₃·6H₂O-catalyzed Friedel–Crafts type benzylations of arenes using simple benzylic alcohols under mild conditions and with high functional group tolerance.⁴ Christoffers et al. studied FeCl₃-catalyzed conjugate additions of 1,3-dicarbonyl compounds to enones.⁵ Beller and co-workers have recently reported the FeCl₃-catalyzed condensation of 1,3-dicarbonyl compounds with simple benzylic alcohols.⁶ A number of related transformations have been studied in recent years.⁷

Despite the preparative utility of these reactions, the direct synthesis of sterically encumbered triarylmethanes and diarylmethanes by Fe-catalyzed benzylation of 1,3-dicarbonyl compounds is problematic. In addition, the synthesis of highly substituted and functionalized products depends on the availability of the starting materials, functionalized and highly substituted arenes. Their regioselective synthesis by electrophilic aromatic substitution reactions can be a very difficult task. An alternative strategy for the synthesis of sterically encumbered and highly functionalized arenes relies on the application of suitable dienes in cyclization reactions (building block approach). Some years ago, Chan et al. developed⁸ a convenient approach to salicylates by formal [3+3] cyclizations⁹ of 1,3-bis(trimethylsilyloxy)-1,3-dienes¹⁰ with 3-trimethylsilyloxy-2-en-1-ones. Herein, we report, for the first time, the synthesis of sterically encumbered and functionalized triarylmethanes by a combined FeCl₃-catalyzed benzylation/[3+3] cyclocondensation approach. The products reported herein are not readily available by other methods and have, to the best of our knowledge, not yet been prepared.

The FeCl₃·6H₂O-catalyzed benzylation of acetylacetone (**1**) with benzylalcohols **1a–e**, following conditions reported by Beller and co-workers,⁶ afforded products **3a–e** in very good yields (Scheme 1, Table 1).¹¹ The silylation of **3a–e** afforded the 3-silyloxy-2-en-1-ones **4a–e**.

The TiCl₄-mediated formal [3+3] cyclocondensation of **4a** with 1,3-bis(silyloxy)-1,3-diene **5a**, available from methyl acetoacetate in two steps,⁸ afforded the triarylmethane **6a** (Scheme 2). During the optimization, it proved to be important to carry out the

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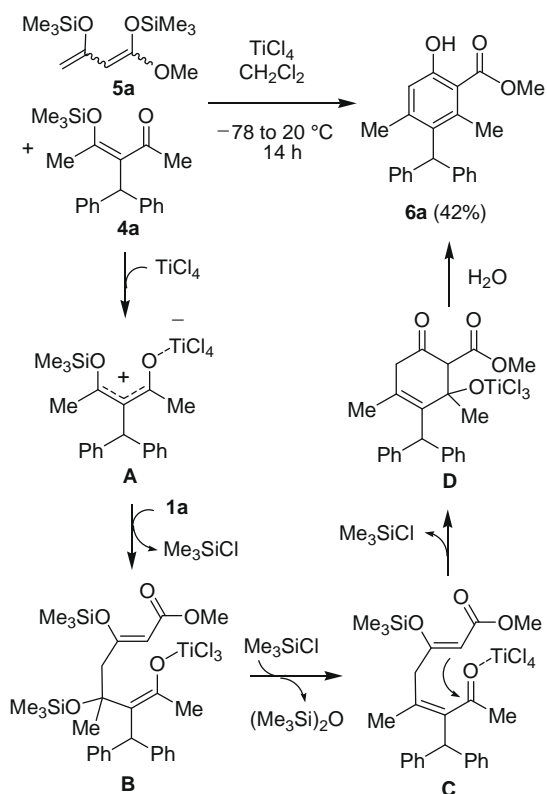


Scheme 1. Synthesis of **4a–e**. Reagents and conditions: (i) $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$, NO_2CH_3 , 50°C , 4 h; (ii) Me_3SiCl , NEt_3 , C_6H_6 , 20°C , 72 h.

Table 1
Synthesis of **3a–e** and **4a–e**

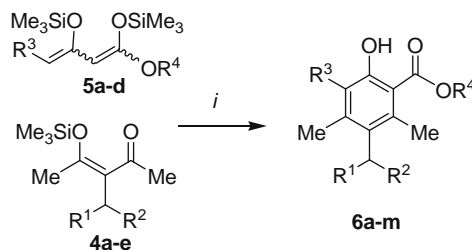
3,4	R ¹	R ²	% (3) ^a	% (4) ^a
a	Ph	Ph	91	90
b	4-(MeO)C ₆ H ₄	4-(MeO)C ₆ H ₄	88	91
c	4-FC ₆ H ₄	4-FC ₆ H ₄	87	89
d	4-ClC ₆ H ₄	4-ClC ₆ H ₄	85	92
e	Me	Ph	94	81

^a Isolated yields.



Scheme 2. Possible mechanism of the formation of **6a**.

reactions in a highly concentrated solution.¹² The formation of **6a** can be explained by reaction of **4a** with TiCl_4 to give intermediate **A**. The attack of the terminal carbon atom of **5a** onto **A** afforded intermediate **B**. The elimination of TMS-siloxane (intermediate **C**) and subsequent cyclization gave intermediate **D**. The elimination of titanium hydroxide (before or during the aqueous work-up)



Scheme 3. Synthesis of **6a–m**. Reagents and conditions: (i) TiCl_4 , CH_2Cl_2 , $-78 \rightarrow 20^\circ\text{C}$, 20 h.

Table 2
Synthesis of biaryls **6a–m**

4	5	6	R ¹	R ²	R ³	R ⁴	% (6) ^a
a	a	a	Ph	Ph	H	Me	42
a	b	b	Ph	Ph	H	Et	45
a	c	c	Ph	Ph	Me	Me	31
a	d	d	Ph	Ph	Et	Me	42
b	a	e	4-(MeO)C ₆ H ₄	4-(MeO)C ₆ H ₄	H	Me	32
b	b	f	4-(MeO)C ₆ H ₄	4-(MeO)C ₆ H ₄	H	Et	37
c	a	g	4-FC ₆ H ₄	4-FC ₆ H ₄	H	Me	33
c	b	h	4-FC ₆ H ₄	4-FC ₆ H ₄	H	Et	37
d	a	i	4-ClC ₆ H ₄	4-ClC ₆ H ₄	H	Me	50
d	b	j	4-ClC ₆ H ₄	4-ClC ₆ H ₄	H	Et	53
d	c	k	4-ClC ₆ H ₄	4-ClC ₆ H ₄	Me	Me	40
d	d	l	4-ClC ₆ H ₄	4-ClC ₆ H ₄	Et	Me	42
e	a	m	Me	Ph	H	Me	55

^a Isolated yields.

and aromatization resulted in the formation of product **6a**. Due to the symmetrical structure of **A**, the attack of **1a** on either terminal allylic carbon atoms would result in the formation of the same product (**6a**).

The TiCl_4 -mediated [3+3] cyclocondensation of **4a–e** with 1,3-bis(silyloxy)-1,3-dienes **5a–d**, available from the corresponding 1,3-dicarbonyl compounds in one or two steps,⁸ afforded the triarylmethanes **6a–m** (Scheme 3, Table 2). During the optimization, it proved to be important to carry out the reactions in a highly concentrated solution.¹¹ The yield of diarylmethane **6m** was higher than the yields of triarylmethanes **6a–l**. The best yields of the triarylmethanes were obtained for derivatives **6i,j**, which are derived from the chloro-substituted benzylalcohol **1d**. The yields of triarylmethanes **6a,b** and **6i,j**, derived from the unsubstituted dienes **5a,b**, were higher than those of products **6c,d** and **6k,l**, which are derived from dienes **5c,d** (containing a substituent located at the terminal carbon atom).

In conclusion, a variety of functionalized and sterically encumbered triarylmethanes were prepared by combination of FeCl_3 -catalyzed benzylations of 1,3-diketones and formal [3+3] cyclocondensation reactions. The products are not readily available by other methods.

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 - In a pressure tube, FeCl₃·6H₂O (5 mol %), 1-phenylethanol (5.0 mmol), and acetylacetone (20.0 mmol) were dissolved in 10 mL of nitromethane. After stirring for 4 h at 50 °C, the reaction was quenched with water followed by extraction with dichloromethane. The combined organic layers were dried over MgSO₄ and the solvents were distilled off. Then, the product was purified by column chromatography (heptanes/ethyl acetate = 1:1).
 - Typical procedure for the synthesis of triarylmethanes 6a–m*: To a CH₂Cl₂ solution (5 mL) of **5a** (236 mg, 1.0 mmol) and **4a** (372 mg, 1.1 mmol) was dropwise added TiCl₄ (0.12 mL, 1.1 mmol) at –78 °C. The reaction mixture was allowed to warm to 20 °C for 6–12 h. After stirring for additional 2–6 h at 20 °C, hydrochloric acid (10%, 20 mL) was added. The organic, and the aqueous layers were separated and the latter was extracted with dichloromethane (3 × 25 mL). The combined organic layers were dried (Na₂SO₄), filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, heptanes/ethyl acetate) to give **6a** as a colorless solid (115 mg, 33%), mp = 153–155 °C. ¹H NMR (250 MHz, CDCl₃): δ 1.98 (s, 3H, CH₃), 2.07 (s, 3H, CH₃), 3.79 (s, 3H, OCH₃), 5.92 (s, 1H, CH), 6.65 (s, 1H, ArH), 6.99–7.26 (m, 10H, Ph), 10.51 (s, 1H, OH). ¹³C NMR (250 MHz, CDCl₃): δ 20.3, 21.7 (CH₃), 49.6 (CH), 50.9 (OCH₃), 111.7 (C), 116.7, 124.9, 127.1, 128.0 (CH_{Ar}), 132.1, 139.3, 141.0, 144.3, 158.8, 170.9 (C). IR (KBr): $\bar{\nu}$ = 2987 (w), 1663 (s), 1564 (m), 1435 (m), 1341 (m), 1210 (s), 1069 (s), 857 (m), 801 (s), 719 (s) 696 (s) cm⁻¹. MS (EI, 70 eV): *m/z* (%) = 346 (M⁺, 66), 314 (100), 299 (21), 237 (18), 165 (49). HRMS (EI): calcd for C₂₃H₂₂O₃ [M]⁺: 346.156966; found: 346.15635.