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Synthesis of functionalized triarylmethanes based on a '$FeCl_3$-catalyzed benzylation/[3+3] cyclocondensation' strategy

Rasheed Ahmad [a], Abdolmajid Riahi [a,b], Peter Langer [a,b,*]

[a] Institut für Chemie, Universität Rostock, Albert-Einstein-Str. 3a, 18059 Rostock, Germany
[b] Leibniz-Institut für Katalyse e. V. an der Universität Rostock, Albert-Einstein-Str. 29a, 18059 Rostock, Germany

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ABSTRACT

Functionalized triarylmethanes are prepared in two steps by $FeCl_3$-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.

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 mohsenone 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 $FeCl_3 \cdot 6H_2O$-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 $FeCl_3$-catalyzed conjugate additions of 1,3-dicarbonyl compounds to enones.[5] Beller and co-workers have recently reported the $FeCl_3$-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. developed[8] a convenient approach to salicylates by formal [3+3] cyclizations[9] of 1,3-bis(trimethylsilyloxy)-1,3-dienes[10] 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 $FeCl_3$-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 $FeCl_3 \cdot 6H_2O$-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 $TiCl_4$-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

* Corresponding author. Tel.: +49 381 4986410; fax: +49 381 4986412.
E-mail address: peter.langer@uni-rostock.de (P. Langer).

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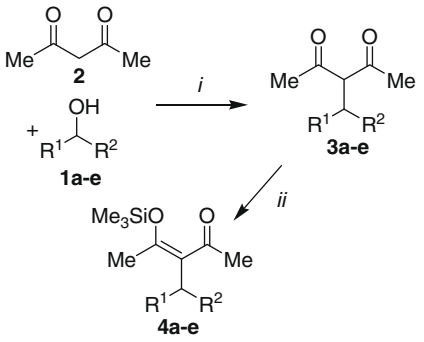
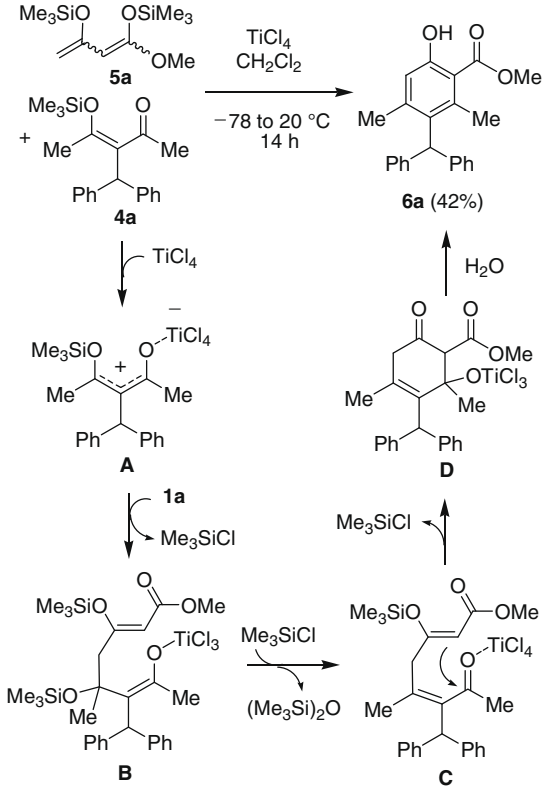


Scheme 1. Synthesis of **4a–e**. Reagents and conditions: (i) $FeCl_3{\cdot}6H_2O$, NO_2CH_3, 50 °C, 4 h; (ii) Me_3SiCl, NEt_3, C_6H_6, 20 °C, 72 h.

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

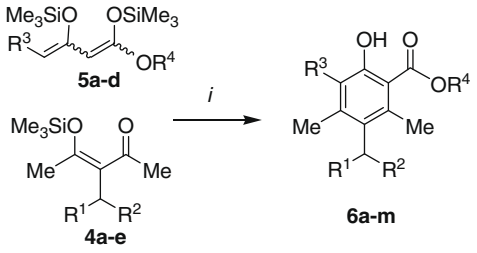
3,4	R^1	R^2	% (**3**)[a]	% (**4**)[a]
a	Ph	Ph	91	90
b	4-(MeO)C_6H_4	4-(MeO)C_6H_4	88	91
c	4-FC_6H_4	4-FC_6H_4	87	89
d	4-ClC_6H_4	4-ClC_6H_4	85	92
e	Me	Ph	94	81

[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→20 °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_6H_4	4-(MeO)C_6H_4	H	Me	32
b	**b**	**f**	4-(MeO)C_6H_4	4-(MeO)C_6H_4	H	Et	37
c	**a**	**g**	4-FC_6H_4	4-FC_6H_4	H	Me	33
c	**b**	**h**	4-FC_6H_4	4-FC_6H_4	H	Et	37
d	**a**	**i**	4-ClC_6H_4	4-ClC_6H_4	H	Me	50
d	**b**	**j**	4-ClC_6H_4	4-ClC_6H_4	H	Et	53
d	**c**	**k**	4-ClC_6H_4	4-ClC_6H_4	Me	Me	40
d	**d**	**l**	4-ClC_6H_4	4-ClC_6H_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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11. In a pressure tube, $FeCl_3{\cdot}6H_2O$ (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 $MgSO_4$ and the solvents were distilled off. Then, the product was purified by column chromatography (heptanes/ethyl acetate = 1:1).
12. *Typical procedure for the synthesis of triarylmethanes* **6a–m**: To a CH_2Cl_2 solution (5 mL) of **5a** (236 mg, 1.0 mmol) and **4a** (372 mg, 1.1 mmol) was dropwise added $TiCl_4$ (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 (Na_2SO_4), 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. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.98 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 5.92 (s, 1H, CH), 6.65 (s, 1H, ArH), 6.99–7.26 (m, 10H, Ph), 10.51 (s, 1H, OH). ^{13}C NMR (250 MHz, $CDCl_3$): δ 20.3, 21.7 (CH_3), 49.6 (CH), 50.9 (OCH_3), 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): $\tilde{\nu} = 2987$ (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 $C_{23}H_{22}O_3$ $[M]^+$: 346.156966; found: 346.15635.