# Synthesis of functionalized triarylmethanes based on a ${ } \mathrm{FeCl}_{3}$-catalyzed benzylation/[3+3] cyclocondensation' strategy 

Rasheed Ahmad ${ }^{\text {a }}$, Abdolmajid Riahi ${ }^{\text {a,b }}$, Peter Langer ${ }^{\text {a,b,* }}$<br>${ }^{\text {a }}$ Institut für Chemie, Universität Rostock, Albert-Einstein-Str. 3a, 18059 Rostock, Germany<br>${ }^{\mathrm{b}}$ Leibniz-Institut für Katalyse e. V. an der Universität Rostock, Albert-Einstein-Str. 29a, 18059 Rostock, Germany

## A R T I C L E I N F O

Article history:
Received 27 November 2008
Revised 12 January 2009
Accepted 14 January 2009
Available online 20 January 2009

## Keywords: <br> Arenes

Catalysis
Cyclizations
Regioselectivity
Silyl enol ethers


#### Abstract

Functionalized triarylmethanes are prepared in two steps by $\mathrm{FeCl}_{3}$-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.


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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, ${ }^{1 \mathrm{a}}$ inhibition of hepatic cholesterol, ${ }^{1 \mathrm{~b}}$ inhibition of aldose reductase $2,{ }^{1 \mathrm{c}}$ antiproliferative activities, ${ }^{1 \mathrm{~d}}$ antiviral and cytotoxic activity, ${ }^{1 \mathrm{e}}$ antifungal activity, ${ }^{1 \mathrm{f}}$ anti-HIV activity, ${ }^{1 g . h}$ and CNS activity. ${ }^{1 i}$ 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 ${ }^{3 \mathrm{a}, 1 \mathrm{~g}}$ and antibacterial activity. ${ }^{3 \mathrm{~b}}$

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 $\mathrm{FeCl}_{3} \cdot 6 \mathrm{H}_{2} \mathrm{O}$-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 $\mathrm{FeCl}_{3}-$ catalyzed conjugate additions of 1,3-dicarbonyl compounds to enones. ${ }^{5}$ Beller and co-workers have recently reported the $\mathrm{FeCl}_{3}-$ catalyzed condensation of 1,3-dicarbonyl compounds with simple benzylic alcohols. ${ }^{6}$ A number of related transformations have been studied in recent years. ${ }^{7}$

[^0]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 $\mathrm{FeCl}_{3}$-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 $\mathrm{FeCl}_{3} \cdot 6 \mathrm{H}_{2} \mathrm{O}$-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-1ones $\mathbf{4 a - e}$.

The $\mathrm{TiCl}_{4}$-mediated formal [3+3] cyclocondensation of $\mathbf{4 a}$ 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


Scheme 1. Synthesis of 4a-e. Reagents and conditions: (i) $\mathrm{FeCl}_{3} \cdot 6 \mathrm{H}_{2} \mathrm{O}, \mathrm{NO}_{2} \mathrm{CH}_{3}$, $50^{\circ} \mathrm{C}, 4 \mathrm{~h}$; (ii) $\mathrm{Me}_{3} \mathrm{SiCl}, \mathrm{NEt}_{3}, \mathrm{C}_{6} \mathrm{H}_{6}, 20^{\circ} \mathrm{C}, 72 \mathrm{~h}$.

Table 1
Synthesis of 3a-e and 4a-e

| $\mathbf{3 , 4}$ | $\mathrm{R}^{1}$ | $\mathrm{R}^{2}$ | $\%(\mathbf{3})^{\mathrm{a}}$ | $\%(\mathbf{4})^{\mathrm{a}}$ |
| :--- | :--- | :--- | :--- | :--- |
| $\mathbf{a}$ | Ph | Ph | 91 | 90 |
| b | $4-(\mathrm{MeO}) \mathrm{C}_{6} \mathrm{H}_{4}$ | $4-(\mathrm{MeO}) \mathrm{C}_{6} \mathrm{H}_{4}$ | 88 | 91 |
| $\mathbf{c}$ | $4-\mathrm{FC}_{6} \mathrm{H}_{4}$ | $4-\mathrm{FC}_{6} \mathrm{H}_{4}$ | 87 | 89 |
| $\mathbf{d}$ | $4-\mathrm{ClC}_{6} \mathrm{H}_{4}$ | $4-\mathrm{ClC}_{6} \mathrm{H}_{4}$ | 85 | 92 |
| $\mathbf{e}$ | Me | Ph | 94 | 81 |

${ }^{\text {a }}$ Isolated yields.


Scheme 2. Possible mechanism of the formation of $\mathbf{6 a}$.
reactions in a highly concentrated solution. ${ }^{12}$ The formation of $\mathbf{6 a}$ can be explained by reaction of $\mathbf{4 a}$ with $\mathrm{TiCl}_{4}$ to give intermediate A. The attack of the terminal carbon atom of $\mathbf{5 a}$ onto $\mathbf{A}$ afforded intermediate $\mathbf{B}$. The elimination of TMS-siloxane (intermediate $\mathbf{C}$ ) and subsequent cyclization gave intermediate $\mathbf{D}$. The elimination of titanium hydroxide (before or during the aqueous work-up)


Scheme 3. Synthesis of 6a-m. Reagents and conditions: (i) $\mathrm{TiCl}_{4}, \mathrm{CH}_{2} \mathrm{Cl}_{2}$, $-78 \rightarrow 20^{\circ} \mathrm{C}, 20 \mathrm{~h}$.

Table 2
Synthesis of biaryls 6a-m

| $\mathbf{4}$ | $\mathbf{5}$ | $\mathbf{6}$ | $\mathrm{R}^{1}$ | $\mathrm{R}^{2}$ | $\mathrm{R}^{3}$ | $\mathrm{R}^{4}$ | $\%(\mathbf{6})^{\text {a }}$ |
| :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- |
| $\mathbf{a}$ | $\mathbf{a}$ | $\mathbf{a}$ | Ph | Ph | H | Me | 42 |
| $\mathbf{a}$ | $\mathbf{b}$ | $\mathbf{b}$ | Ph | Ph | H | Et | 45 |
| $\mathbf{a}$ | $\mathbf{c}$ | $\mathbf{c}$ | Ph | Ph | Me | Me | 31 |
| $\mathbf{a}$ | $\mathbf{d}$ | $\mathbf{d}$ | Ph | Ph | Et | Me | 42 |
| $\mathbf{b}$ | $\mathbf{a}$ | $\mathbf{e}$ | $4-(\mathrm{MeO}) \mathrm{C}_{6} \mathrm{H}_{4}$ | $4-(\mathrm{MeO}) \mathrm{C}_{6} \mathrm{H}_{4}$ | H | Me | 32 |
| $\mathbf{b}$ | $\mathbf{b}$ | $\mathbf{f}$ | $4-(\mathrm{MeO}) \mathrm{C}_{6} \mathrm{H}_{4}$ | $4-(\mathrm{MeO}) \mathrm{C}_{6} \mathrm{H}_{4}$ | H | Et | 37 |
| $\mathbf{c}$ | $\mathbf{a}$ | $\mathbf{g}$ | $4-\mathrm{FC}_{6} \mathrm{H}_{4}$ | $4-\mathrm{FC}_{6} \mathrm{H}_{4}$ | H | Me | 33 |
| $\mathbf{c}$ | $\mathbf{b}$ | $\mathbf{h}$ | $4-\mathrm{FC}_{6} \mathrm{H}_{4}$ | $4-\mathrm{FC}_{6} \mathrm{H}_{4}$ | H | Et | 37 |
| $\mathbf{d}$ | $\mathbf{a}$ | $\mathbf{i}$ | $4-\mathrm{Cl}_{6} \mathrm{H}_{4}$ | $4-\mathrm{Cl}_{6} \mathrm{H}_{4}$ | H | Me | 50 |
| $\mathbf{d}$ | $\mathbf{b}$ | $\mathbf{j}$ | $4-\mathrm{Cl}_{6} \mathrm{H}_{4}$ | $4-\mathrm{ClC}_{6} \mathrm{H}_{4}$ | H | Et | 53 |
| $\mathbf{d}$ | $\mathbf{c}$ | $\mathbf{k}$ | $4-\mathrm{ClC}_{6} \mathrm{H}_{4}$ | $4-\mathrm{ClC}_{6} \mathrm{H}_{4}$ | Me | Me | 40 |
| $\mathbf{d}$ | $\mathbf{d}$ | $\mathbf{l}$ | $4-\mathrm{ClC}_{6} \mathrm{H}_{4}$ | $4-\mathrm{ClC}_{6} \mathrm{H}_{4}$ | Et | Me | 42 |
| $\mathbf{e}$ | $\mathbf{a}$ | $\mathbf{m}$ | Me | Ph | H | Me | 55 |

${ }^{\text {a }}$ Isolated yields.
and aromatization resulted in the formation of product 6a. Due to the symmetrical structure of $\mathbf{A}$, the attack of $\mathbf{1 a}$ on either terminal allylic carbon atoms would result in the formation of the same product ( $\mathbf{6 a}$ ).

The $\mathrm{TiCl}_{4}$-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 $\mathbf{6 a - m}$ (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 $\mathbf{6 m}$ was higher than the yields of triarylmethanes $\mathbf{6 a - l}$. The best yields of the triarylmethanes were obtained for derivatives $\mathbf{6 i} \mathbf{j}$, which are derived from the chloro-substituted benzylalcohol 1d. The yields of triarylmethanes $\mathbf{6 a , b}$ and $\mathbf{6 i} \mathbf{i} \mathbf{j}$, derived from the unsubstituted dienes $\mathbf{5 a}, \mathbf{b}$, were higher than those of products $\mathbf{6 c}, \mathbf{d}$ and $\mathbf{6 k}, \mathbf{1}$, which are derived from dienes $\mathbf{5 c}$,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 $\mathrm{FeCl}_{3}$-catalyzed benzylations of 1,3 -diketones and formal [3+3] cyclocondensation reactions. The products are not readily available by other methods.

## Acknowledgement

Financial support from the State of Pakistan (HEC scholarship for R.A.) is gratefully acknowledged.

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11. In a pressure tube, $\mathrm{FeCl}_{3} \cdot 6 \mathrm{H}_{2} \mathrm{O}(5 \mathrm{~mol} \%)$, 1-phenylethanol ( 5.0 mmol ), and acetylacetone ( 20.0 mmol ) were dissolved in 10 mL of nitromethane. After stirring for 4 h at $50^{\circ} \mathrm{C}$, the reaction was quenched with water followed by extraction with dichloromethane. The combined organic layers were dried over $\mathrm{MgSO}_{4}$ 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 $\mathbf{6 a - m}$ : $\mathrm{To} \mathrm{a} \mathrm{CH}_{2} \mathrm{Cl}_{2}$ solution $(5 \mathrm{~mL})$ of $\mathbf{5 a}(236 \mathrm{mg}, 1.0 \mathrm{mmol})$ and $\mathbf{4 a}(372 \mathrm{mg}, 1.1 \mathrm{mmol})$ was dropwise added $\mathrm{TiCl}_{4}(0.12 \mathrm{~mL}, 1.1 \mathrm{mmol})$ at $-78^{\circ} \mathrm{C}$. The reaction mixture was allowed to warm to $20^{\circ} \mathrm{C}$ for $6-12 \mathrm{~h}$. After stirring for additional $2-6 \mathrm{~h}$ at $20^{\circ} \mathrm{C}$, hydrochloric acid ( $10 \%, 20 \mathrm{~mL}$ ) was added. The organic, and the aqueous layers were separated and the latter was extracted with dichloromethane $(3 \times 25 \mathrm{~mL})$. The combined organic layers were dried $\left(\mathrm{Na}_{2} \mathrm{SO}_{4}\right)$, filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, heptanes/ethyl acetate) to give $\mathbf{6 a}$ as a colorless solid ( $115 \mathrm{mg}, 33 \%$ ), $\mathrm{mp}=153-155^{\circ} \mathrm{C} .{ }^{1} \mathrm{H}$ NMR ( $250 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 1.98(\mathrm{~s}, 3 \mathrm{H}$, $\mathrm{CH}_{3}$ ), $2.07\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3}\right), 3.79\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 5.92(\mathrm{~s}, 1 \mathrm{H}, \mathrm{CH}), 6.65(\mathrm{~s}, 1 \mathrm{H}, \mathrm{ArH})$, 6.99-7.26 (m, 10H, Ph), $10.51(\mathrm{~s}, 1 \mathrm{H}, \mathrm{OH}) .{ }^{13} \mathrm{C}$ NMR ( $250 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 20.3$, $21.7\left(\mathrm{CH}_{3}\right), 49.6(\mathrm{CH}), 50.9\left(\mathrm{OCH}_{3}\right), 111.7(\mathrm{C}), 116.7,124.9,127.1,128.0\left(\mathrm{CH}_{\mathrm{Ar}}\right)$, 132.1, 139.3, 141.0, 144.3, 158.8, 170.9 (C). IR (KBr): $\tilde{v}=2987$ (w), 1663 (s), 1564 (m), 1435 (m), 1341 (m), 1210 (s), 1069 ( s), 857 (m), 801 ( s$), 719$ (s) 696 (s) $\mathrm{cm}^{-1}$. MS (EI, 70 eV ): $m / z(\%)=346\left(\mathrm{M}^{+}, 66\right), 314(100), 299(21), 237(18)$, 165 (49). HRMS (EI): calcd for $\mathrm{C}_{23} \mathrm{H}_{22} \mathrm{O}_{3}[\mathrm{M}]^{+}: 346.156966$; found: 346.15635.


[^0]:    * Corresponding author. Tel.: +49 3814986410 ; fax: +49 3814986412.

    E-mail address: peter.langer@uni-rostock.de (P. Langer).

