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Domino 'Michael-retro-Michael-aldol' reactions of 1,3-bis-silyl enol ethers with 3-formylchromones

Peter Langer* and Bettina Appel

Institut für Chemie und Biochemie der Ernst-Moritz-Arndt-Universität Greifswald, Soldmannstr. 16, D-17487 Greifswald, Germany

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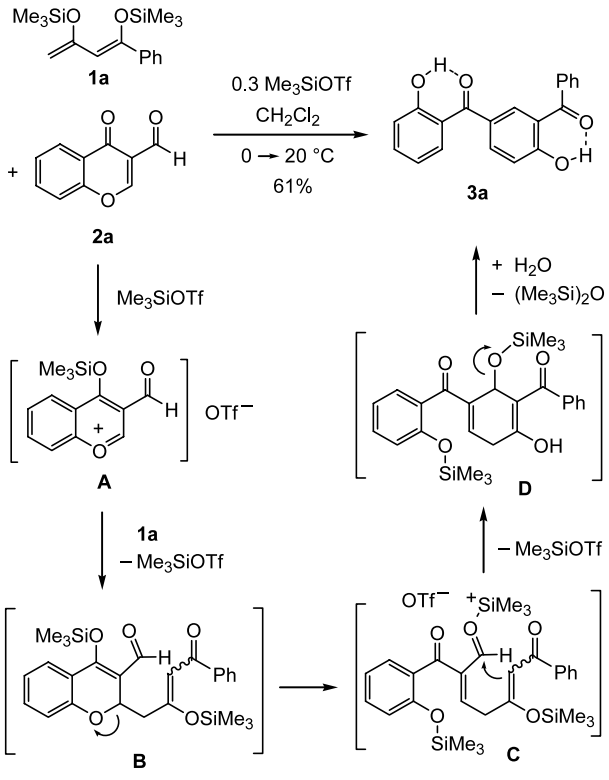
Abstract—Functionalized benzophenones were prepared by domino 'Michael-retro-Michael-aldol' reactions of 1,3-bis-silyl enol ethers with 3-formylchromones.

Functionalized benzophenones are of considerable interest as pharmacologically relevant natural products and natural product analogues and represent versatile synthetic building blocks.[1,2] Classical syntheses of benzophenone derivatives mainly rely on the Friedel–Crafts acylation.[3] However, unsatisfactory results are frequently obtained when this method is applied to the synthesis of functionalized or substituted derivatives. Major drawbacks result from the drastic reaction conditions and from the low chemo- and regioselectivity. Therefore there is a need for the development of alternative methods which allow the convenient and selective synthesis of a wide range of functionalized benzophenones under mild conditions.[4,5] We have recently reported the base-mediated synthesis of 4-(2′-hydroxybenzoyl)salicylic esters from (2,4-dioxobutylidene)triphenylphosphoranes.[6] Unfortunately, the preparative scope of this method is severely limited by the fact that substituted, functionalized and 1,3-diketone derived phosphoranes are not readily available. In addition, the reactivity of substituted phosphoranes is very low and their application to the synthesis of benzophenones was unsuccessful. Herein, we wish to report a new and more general method for the synthesis of functionalized benzophenones. This methodology relies on what is, to the best of our knowledge, the first domino 'Michael-retro-Michael-aldol' reactions[7] of 1,3-bis-silyl enol ethers[8,9] with 3-formylchromones.[10–12] These reactions allow a convenient, regio- and chemoselective synthesis of a great variety of functionalized benzophenones from readily available starting materials.



Scheme 1. Synthesis of functionalized benzophenone **3a**.

Keywords: benzophenones; cyclizations; chromones; domino reactions; silyl enol ethers.

* Corresponding author. Fax: (+49) 3834-864373; e-mail: peter.langer@uni-greifswald.de

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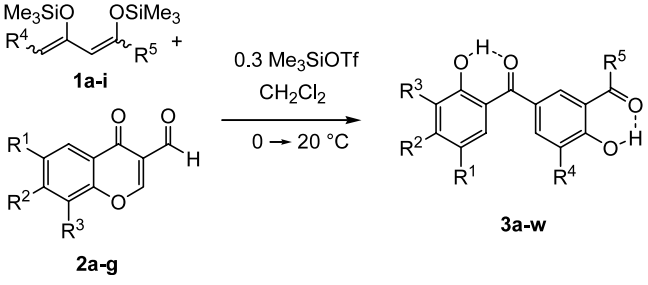
Our starting point was the development of a new method for the synthesis of the interesting benzoyl substituted benzophenone **3a**. Complex mixtures were obtained in the reaction of chromone **2a** with the dianion of benzoylacetone. The problem was solved by employment of the 1,3-bis-silyl enol ether **1a** which is available from benzoylacetone in one or two steps.[8b] The reaction of **1a** with **2a** in the presence of TMSOTf afforded the desired benzophenone **3a**.[13] During the optimization of the reaction, the use of TMSOTf (0.3 equiv.) proved to be an important parameter.[10o] The use of stoichiometric amounts of the Lewis acid did not result in an increase of the yield. The reaction was very robust against minor changes of the conditions (reaction time and temperature).

The formation of **3a** can be explained by a domino 'Michael-retro-Michael-aldol' reaction (Scheme 1). The reaction of 3-formylchromone with TMSOTf afforded the benzopyrylium triflate **A**. The reaction of **A** with the terminal carbon atom of **1a** gave intermediate **B** which underwent a retro-Michael reaction to give the polyketide **C**. An intramolecular aldol reaction afforded intermediate **D** which was transformed into the product **3a** by elimination of siloxane.

To study the preparative scope of our methodology the substituents of the starting materials were systematically varied (Scheme 2, Table 1). The reaction of benzoylacetone derived 1,3-bis-silyl enol ether **1a** with chloro-substituted 3-formylchromone **2b** afforded the functionalized benzophenone **3b** with very good chemoselectivity. The cyclization of 1,3-bis-silyl enol ether **1b**, prepared from acetylacetone, with **2a** and **2b** afforded the acetyl-substituted benzophenones **3c** and **3d**, respectively. The ethoxycarbonyl substituted benzophenones **3e–g** were prepared from the ethyl acetoacetate-derived silyl enol ether **1c**. The reaction of 3-formylchromone **2a** with 1,3-bis-silyl enol ether **1d**, containing a methyl group at the terminal carbon atom, afforded the methyl-substituted benzoylacetone **3h**. The cyclization of the ethyl-substituted silyl enol ether **1e**, prepared from ethyl 3-oxohexanoate, with 3-formylchromones **2a–g** afforded the respective substituted benzophenones **3i–o**. The allyl-, *n*-butyl-, *n*-octyl- and benzyl-substituted benzophenones **3p–w** were prepared by cyclization of the corresponding 1,3-bis-silyl enol ethers **1f–i** with the 3-formylchromones **2a**,**b**,**d**. All cyclization reactions proceeded with very good chemoselectivity.



Scheme 2. Synthesis of the functionalized benzophenones **3a–w**.

Table 1. Products and yields

1	2	3	R^1	R^2	R^3	R^4	R^5	3 (%)[a]
a	**a**	**a**	H	H	H	H	Ph	61
a	**b**	**b**	Cl	H	Cl	H	Ph	55
b	**a**	**c**	H	H	H	H	Me	43
b	**b**	**d**	Cl	H	Cl	H	Me	52
c	**a**	**e**	H	H	H	H	OEt	51
c	**c**	**f**	Cl	H	H	H	OEt	46
c	**b**	**g**	Cl	H	Cl	H	OEt	82
d	**a**	**h**	H	H	H	Me	OMe	56
e	**a**	**i**	H	H	H	Et	OEt	53
e	**b**	**j**	Cl	H	Cl	Et	OEt	42
e	**d**	**k**	Me	H	Me	Et	OEt	46
e	**e**	**l**	Cl	Me	H	Et	OEt	51
e	**c**	**m**	Cl	H	H	Et	OEt	55
e	**f**	**n**	Br	H	Br	Et	OEt	54
e	**g**	**o**	NO_2	H	H	Et	OEt	63
f	**a**	**p**	H	H	H	Allyl	OEt	42
f	**d**	**q**	Me	H	Me	Allyl	OEt	47
f	**b**	**r**	Cl	H	Cl	Allyl	OEt	44
g	**a**	**s**	H	H	H	*n*-Butyl	OEt	68
g	**b**	**t**	Cl	H	Cl	*n*-Butyl	OEt	43
h	**a**	**u**	H	H	H	*n*-Octyl	OEt	43
h	**b**	**v**	Cl	H	Cl	*n*-Octyl	OEt	56
i	**a**	**w**	H	H	H	Bn	OEt	48

[a] Yields of isolated products.

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13. Synthesis of (2-hydroxyphenyl)-(3′-acetyl-4′-hydroxyphenyl)-methanone **3c**: To a CH_2Cl_2 solution (10 ml) of 3-formylchromone **2a** (200 mg, 1.15 mmol) was added Me_3SiOTf (0.06 ml, 0.35 mmol) at 0°C. After stirring for 1 h at 20°C, CH_2Cl_2 (10 ml) and **1b** (365 mg, 1.50 mmol) were added at 0°C. The mixture was stirred for 12 h at 20°C and subsequently poured into an aqueous solution of hydrochloric acid (10%, 80 ml). The organic and the aqueous layer were separated and the latter was extracted with ether (3×80 ml). The combined organic layers were washed with water, dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, EtOAc/*n*-hexane = 1:15) to give **3c** as a colourless solid (127 mg, 43%). ^1H NMR ($CDCl_3$, 300 MHz): δ 2.69 (s, 3H, CH_3), 6.92 (m, 1H, 5-H), 7.09 (d, $^3J = 8.7$ Hz, 1H, 5′-H), 7.10 (dd, $^3J = 9.2$ Hz, $^4J = 0.8$ Hz, 1H, 3-H), 7.53 (m, 1H, 4-H), 7.58 (dd, $^3J = 9.6$ Hz, $^4J = 1.6$ Hz, 1H, 6-H), 7.86 (dd, $^3J = 8.7$ Hz, $^4J = 2.1$ Hz, 1H, 6′-H), 8.21 (d, $^4J = 2.1$ Hz, 1H, 2′-H), 11.78 (s, 1H, OH), 12.68 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 26.76 (CH_3), 118.50, 118.70, 118.80 (CH), 119.01, 119.27, 128.82 (C), 132.75, 133.21, 136.33, 137.40 (CH), 163.05, 165.52 (C-OH), 198.88, 204.47 (C=O). IR (KBr, cm^{-1}): $\tilde{\nu}$ 3081 (m), 2973 (m), 2925 (m), 1644 (s), 1626 (s), 1588 (s), 1482 (m), 1440 (m), 1423 (m), 1363 (s), 1295 (s), 1241 (s), 1221 (s). λ_{max} (CH_3CN, nm, log ε): 425 (3.16), 403 (3.17), 323 (3.93), 285 (4.02), 250 (4.30). *m*/*z* (EI, 70 eV): 256 (M^+, 100), 241 (20), 213 (15), 163 (23), 145 (10), 121 (90). Calcd. for $C_{15}H_{12}O_4$ (256.1): C 70.31, H 4.72; found C 70.04, H 4.89. All new compounds gave satisfactory spectroscopic and analytical and/or high resolution mass data.