‘Michael–Michael–Wittig’ Reactions of (2,4-Dioxobutylidene)phosphoranes with 3-Formylchromones

Peter Langer,* Edith Holtz

Institut für Chemie und Biochemie der Ernst-Moritz-Arndt-Universität Greifswald, Soldmannstrasse 16, 17487 Greifswald, Germany
E-mail: peter.langer@uni-greifswald.de

Received 5 January 2003

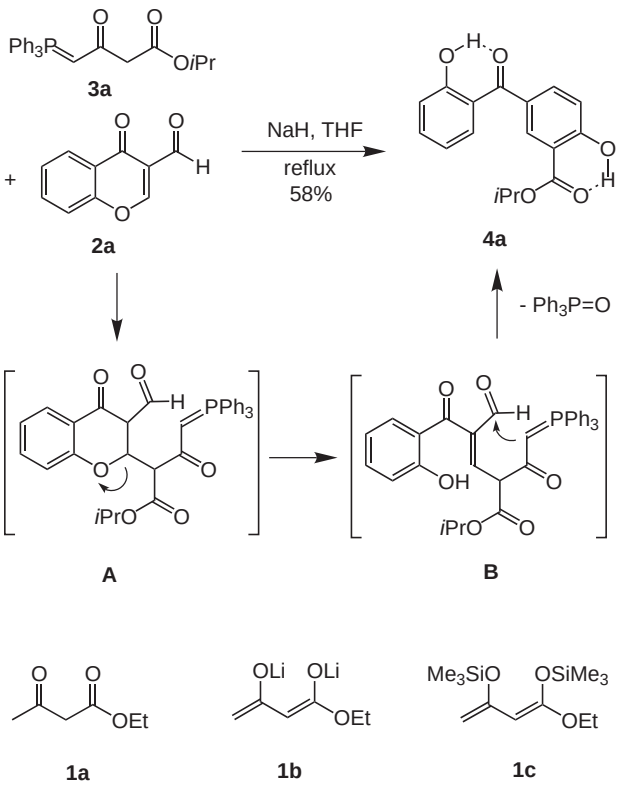
Abstract: 4-(2′-Hydroxybenzoyl)salicylic esters and amides were prepared by domino ‘Michael–retro-Michael–Wittig’ reactions of (2,4-dioxobutylidene)triphenylphosphoranes with 3-formylchromones.

Key words: Michael–Michael–Wittig-reaction, 4-(2′-hydroxybenzoyl)salicylic esters, 4-(2′-hydroxybenzoyl)salicylic amides, (2,4-dioxobutylidene)triphenylphosphoranes

Salicylic derivatives are of pharmacological relevance and possess industrial applications. This includes natural products, such as salicylic acid, various salicylic esters and salicylic glycosides (e.g. salicortin), and synthetic compounds (e. g. aspirin©).[1] In this context, the development of new syntheses of (2′-hydroxybenzoyl)salicylic esters is of considerable interest, since they represent fragments and potential synthetic building blocks of a variety of pharmacologically relevant natural products, such as anthracyclines, pyoluteorin, pyrrolomycines, anthranoids[2] and their analogues.[3]

A number of classic syntheses of benzoylsalicylic derivatives use Friedel–Crafts acylations.[4a] The regioselectivity and yields of this approach are sometimes limited by the drastic reaction conditions required. Interesting alternative approaches rely, for example, on SmI_2 mediated coupling reactions of benzaldehydes with benzylhalides and subsequent oxidation.[4b] A number of functionalized salicylic esters have been prepared by cyclization of 1,3-bis-silyl enol ethers with 1,3-dicarbonyl dielectrophiles and related methods.[4c–4f] Herein, we wish to report a new and efficient synthesis of a variety of 4-(2′-hydroxybenzoyl)salicylic derivatives by domino ‘Michael–retro-Michael–Wittig’ reactions[5] of (2,4-dioxobutylidene)triphenylphosphoranes with 3-formylchromones (4-oxo-4*H*-1-benzopyran-3-carboxaldehydes).[6,7] All reactions proceed with excellent regioselectivity and use readily available starting materials.

The reaction of 3-formylchromone (**2a**) with 1,3-dicarbonyl compounds resulted in attack of the central carbon atom of the nucleophile onto the aldehyde (aldol condensation) and formation of open-chain products.[8] In specific cases a domino cyclization with ring opening of the chromone system was observed. Our first attempts to realize a cyclization of **2a** with acetoacetate d[4] synthons were unsuccessful. The reaction of **2a** with the dianion **1b** of ethyl acetetoacetate (**1a**) resulted in formation of complex mixtures under a variety of conditions. The problem



Scheme 1 Synthesis of 4-(2′-hydroxybenzoyl)salicylic ester **4a**

Table 1 Optimization of the Synthesis of **4a**

Solvent	t (h)	Base	Conditions	Yield (%)[b]
MeOH	48	NaOMe	Reflux	0
THF	21	NaH	20 °C	23
THF	3 + 18[a]	NaH	Reflux	32
THF	8 + 18[a]	NaH	Reflux	51
THF	24	NaH	Reflux	58
THF	24	K_2CO_3	Reflux	13

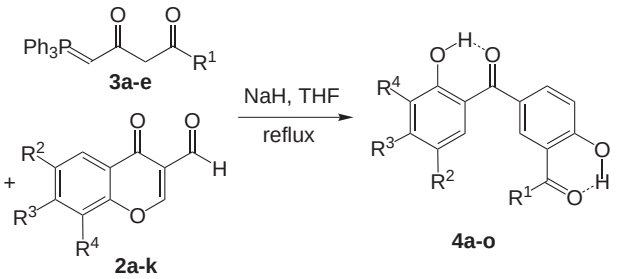
[a] Reflux + 20 °C.
[b] Isolated yield.

Synlett 2003, No. 3, Print: 19 02 2003.
Art Id.1437-2096,E;2003,0,02,0402,0404,ftx,en;D21502ST.pdf.

ISSN 0936-5214

was eventually solved by employment of phosphorane **3a**, which is readily available from *iso*propoxy 4-chloroacetoacetate. The reaction of 3-formylchromone with **3a** afforded 4-(2′-hydroxybenzoyl)salicylic ester **4a** (Scheme 1). During optimization of the reaction the following parameters proved important (Table 1): a) the presence of sodium hydride (NaH), b) employment of THF as the solvent and c) the reaction time (24 h) and temperature (reflux).[9] Extension of the reaction time to 48 hours did not result in any increase of the yield. The Me_3SiOTf catalyzed reaction of **2a** with 1,3-bis-silyl enol ether **1c**, an electroneutral equivalent of **1b**, also resulted in formation of **4a**, however, in low yield.

The formation of **4a** can be explained by a domino 'Michael–retro-Michael–Wittig' reaction. Michael reaction of **2a** with the central carbon atom of **3a** afforded intermediate **A**, which underwent a retro-Michael reaction to give intermediate **B**. The latter underwent an intramolecular Wittig reaction to give **4a** (Scheme 1). The reaction proceeded with very good regioselectivity which can be explained as follows: a) In the first step, the Michael reaction predominated over any aldol or Wittig pathway; b) the 2′-hydroxybenzoyl moiety of **4a** was regiospecifically formed by cleavage of the chromone system; c) the salicylic moiety was formed by regioselective cyclization. The structure of **4a** was established by spectroscopic means. The two intramolecular hydrogen bonds O–H···O could be detected by ^1H NMR.



Scheme 2 Synthesis of 4-(2′-hydroxybenzoyl)salicylic derivatives **4a–o**

To study the preparative scope of our methodology the substituents of the starting materials were systematically varied (Scheme 2, Table 2). The cyclization of 3-formylchromone (**2a**) with ethoxy and methoxy substituted phosphanes **3b** and **3c** gave the corresponding salicylic esters **4b** and **4c**, respectively. The cyclization of **2a** with amino-substituted phosphanes **3d**,**e** afforded the salicylic amides **4d**,**e**. Variation of the chromone moiety was next studied. The reaction of phosphane **3c** with alkyl substituted formylchromones **2b–e** afforded 4-(2′-hydroxybenzoyl)salicylic esters **4f–i**. Salicylic esters **4j–n** were prepared by reaction of **3c** with chloro and bromo substituted chromones **2f–j**. Starting with **2k**, nitro substituted salicylic ester **4o** was obtained.

Table 2 Products and Yields

2	3	4	R^1	R^2	R^3	R^4	%[a]
a	**a**	**a**	O-*i*-Pr	H	H	H	58
a	**b**	**b**	OEt	H	H	H	52
a	**c**	**c**	OMe	H	H	H	55
a	**d**	**d**	$N(CH_2)_4$	H	H	H	54
a	**e**	**e**	NH_2	H	H	H	18
b	**c**	**f**	OMe	Me	H	H	53
c	**c**	**g**	OMe	Et	H	H	55
d	**c**	**h**	OMe	*i*-Pr	H	H	64
e	**c**	**i**	OMe	Me	H	Me	60
f	**c**	**j**	OMe	Cl	H	H	53
g	**c**	**k**	OMe	Br	H	H	56
h	**c**	**l**	OMe	Cl	H	Cl	55
i	**c**	**m**	OMe	Br	H	Br	51[b]
j	**c**	**n**	OMe	Cl	Me	H	58
k	**c**	**o**	OMe	NO_2	H	H	16[c]

[a] Isolated yield.
[b] Isolated in form of the free acid.
[c] Reaction time: 4 h: 16%, 24 h: 0%

Acknowledgment

P. L. thanks Professor A. de Meijere for his support. Financial support from the Fonds der Chemischen Industrie e. V. (Liebig-scholarship for P. L.) and from the Deutsche Forschungsgemeinschaft (Heisenberg-scholarship for P. L. and Normalverfahren) is gratefully acknowledged.

References

(1) *Römpp Lexikon Naturstoffe*; Steglich, W.; Fugmann, B.; Lang-Fugmann, S., Eds.; Thieme: Stuttgart, **1997**.
(2) (a) Ezaki, N.; Shomura, T.; Koyama, M.; Niwa, T.; Kojima, M.; Inouye, S.; Niida, T. *J. Antibiot.* **1981**, *34*, 1363. (b) Kaneda, M.; Nakamura, S.; Ezaki, N.; Iitaka, Y. *J. Antibiot.* **1981**, *34*, 1366. (c) Ezaki, N.; Koyama, M.; Shomura, T.; Tsuruoka, T.; Inouye, S. *J. Antibiot.* **1983**, *36*, 1263. (d) Carter, G. T.; Nietsche, J. A.; Goodman, J. J.; Torrey, M. J.; Dunne, T. S.; Siegel, M. M.; Borders, D. B. *J. Chem. Soc., Chem. Commun.* **1989**, 1271.
(3) (a) Müller, K.; Leukel, P.; Ziereis, K.; Gawlik, I. *J. Med. Chem.* **1994**, *37*, 1660. (b) Barton, D. H. R.; Challis, J. A.; Magnus, P. D.; Marshall, J. P. *J. Chem. Soc. C* **1971**, 2241.
(4) (a) Buchta, E.; Egger, H. *Chem. Ber.* **1957**, *90*, 2760. (b) Shiue, J.-S.; Lin, M.-H.; Fang, J.-M. *J. Org. Chem.* **1997**, *62*, 4643. (c) Chan, T. H.; Brownbridge, P. *J. Am. Chem. Soc.* **1980**, *102*, 3534. (d) Lee, S. D.; Chan, T. H. *Tetrahedron* **1984**, *40*, 3611. (e) Kang, G. J.; Chan, T. H. *J. Org. Chem.* **1985**, *50*, 452. (f) For the synthesis of salicylic derivatives by reactions of 1,3-dicarbonyl dianions, see for

example: Harris, T. M.; Wittek, P. J. *J. Am. Chem. Soc.* **1975**, *97*, 3270. (g) For the reaction of dimethyl 1,3-acetonedicarboxylate with alkynals and alkynones, see: Covarrubias-Zúniga, A.; Ríos-Barrios, E. *J. Org. Chem.* **1997**, *62*, 5688; and references cited therein.

(5) For reviews of domino reactions, see: (a) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131; *Angew. Chem.* **1993**, *105*, 137. (b) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115.

(6) For related cyclization reactions of 3-formylchromones, see: (a) Nohara, A.; Umetani, T.; Sanno, Y. *Tetrahedron* **1974**, *30*, 3553. (b) Jones, W. D.; Albrecht, W. L. *J. Org. Chem.* **1976**, *41*, 706. (c) The cyclization of 3-formyl-chromones with formamidine and amidines afforded 5-(2-hydroxybenzoyl)-pyrimidines: Löwe, W. *Synthesis* **1976**, 274. (d) See also: Petersen, U.; Heitzer, H. *Liebigs Ann. Chem.* **1976**, 1663. (e) With enamines: Heber, D. *Synthesis* **1978**, 691. (f) With hydrazines: Eiden, F.; Haverland, H. *Arch. Pharm. (Weinheim, Ger.)* **1968**, *301*, 819. (g) See also: Ghosh, C. K.; Mukhopadhyay, K. K. *J. Ind. Chem. Soc.* **1978**, *55*, 386. (h) With $H_2NOH{\cdot}HCl$: Hsung, R. P.; Zificsak, C. A.; Wei, L.-L.; Zehnder, L. R.; Park, F.; Kim, M.; Tran, T.-T. T. *J. Org. Chem.* **1999**, *64*, 8736. (i) With *o*-phenylenediamine: Ghosh, C. K.; Khan, S. *Synthesis* **1980**, 701. (j) For conversions into pyrroles and thiophenes: Fitton, A. O.; Frost, J. R.; Suschitzky, H.; Hougton, P. G. *Synthesis* **1977**, 133. (k) For a review on 3-formylchromones, see: Ellis, G. P. *Heterocyclic Compounds*, Vol. 35; Weisberger, A., Ed.; Wiley-Interscience: New York, **1977**, 921.

(7) For phosphorane **3b**, see: (a) Hatanaka, M.; Tanaka, Y.; Ueda, I. *Tetrahedron Lett.* **1995**, 3719. (b) Banwell, M. G.; Cameron, J. M. *Tetrahedron Lett.* **1996**, 525. (c) Hatanaka, M.; Ishida, A.; Tanaka, Y.; Ueda, I. *Tetrahedron Lett.* **1996**, 401. (d) Ceccarelli, S.; Piarulli, U.; Gennari, C. *Tetrahedron Lett.* **1999**, 153.

(8) (a) Ghosh, C. K.; Khan, S. *Synthesis* **1981**, 903. (b) Hass, G.; Stanton, J. L.; von Sprecher, A.; Wenk, P. *J. Heterocycl. Chem.* **1981**, *18*, 607. (c) Prousek, J. *Collect. Czech. Chem. Commun.* **1991**, 1361. (d) Ghosh, C. K.; Bandyopadhyay, C.; Biswas, S.; Chakravarty, A. K. *Ind. J. Chem., Sect. B* **1990**, *29*, 814. (e) Bandyopadhyay, C.; Sur, K. R.; Patra, R. *J. Chem. Res., Synop.* **1998**, *12*, 802.

(9) **Representative Experimental Procedure:** A THF suspension (5 mL) of NaH (78 mg, 3.25 mmol) and **3b** (556 mg, 1.43 mmol) was stirred under nitrogen atmosphere at 0 °C for 30 min. A THF solution (10 mL) of **2a** (190 mg, 1.1 mmol) was added and the solution was stirred for 60 min at 0 °C. The reaction mixture was refluxed for 24 h, cooled and subsequently stirred for 12 h at 20 °C. To the mixture was added diethyl ether (30 mL), an aqueous solution of HCl (5 mL, 1 M) and a saturated solution of NaCl. The aqueous layer was separated and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent of the filtrate was removed in vacuo. The residue was purified by column chromatography (silica gel, diethyl ether/petroleum ether = 1:20) to give **4b** (52%) as a yellow solid. Spectroscopic data of **4b**: ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.42 (t, ^3J = 7 Hz, 3 H, CH_3), 4.45 (q, ^3J = 7 Hz, 2 H, OCH_2CH_3), 6.91 (dd, $^3J_1$ = 7 Hz, $^3J_2$ = 8 Hz, 1 H, Ar), 7.08 (d, ^3J = 8 Hz, 1 H, Ar), 7.10 (d, ^3J = 8 Hz, 1 H, Ar), 7.53 (dd, $^3J_1$ = 7 Hz, $^3J_2$ = 8 Hz, 1 H, Ar), 7.59 (d, ^3J = 8 Hz, 1 H, Ar), 7.84 (d, ^3J = 8 Hz, 1 H, Ar), 8.30 (s, 1 H, Ar), 11.34 (s, 1 H, OH), 11.87 (s, 1 H, OH). ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 14.15 (CH_3), 62.07 (CH_2), 112.47, 119.03, 129.00 (C, Ar, *ortho* and *para* to OH), 117.74, 118.51, 118.70 (CH, Ar, *ortho* and *para* to OH), 132.36, 132.95, 136.18, 136.59 (CH, Ar, *meta* to OH), 163.00, 164.70, 169.61 (C, C–OH, CO_2Et), 199.12 (C, CO). IR (KBr): 3178 (w), 3059 (w), 2987 (w), 2933 (w), 1683 (s), 1629 (s), 1589 (s), 1467 (m), 1444 (m), 1397 (m), 1343 (s), 1293 (s), 1262 (s), 1242 (s), 1176 (m), 1084 (m) cm^{-1}. MS (70 eV): *m/z* (%) = 286 (100) [M$^+$], 121(94). Anal. Calcd for $C_{16}H_{14}O_5$: C, 67.31; H, 4.93. Found: C, 66.88; H, 5.18. All compounds gave satisfactory spectroscopic and analytical and/or high resolution mass data.