A Simple Two Steps Ytterbium Triflate-Catalysed Preparation of 2,2-Dimethyl-2*H*-chromenes from Salicylaldehydes and 2-Methylpropene

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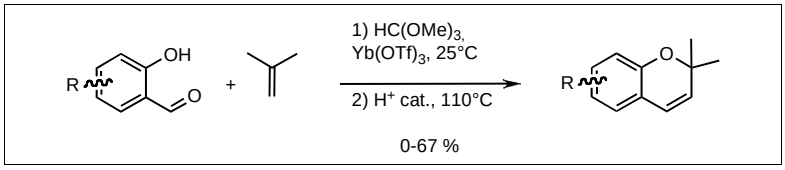

The preparation of various 2,2-dimethyl-2*H*-chromenes was achieved in two steps *via* an ytterbium triflate-catalysed reaction between salicylaldehydes, trimethylorthoformate and 2-methylpropene. From salicylaldehyde, two reaction products were characterised: 4-methoxy-2,2-dimethylchroman and 2-(1,3-dimethoxy-3-methylbutyl)phenol. The former compound probably results from a Lewis acid-catalysed [2+4] cycloaddition between the intermediate quinonemethide and 2-methylpropene whereas the latter may occur *via* a reaction related to a carbonyl-ene reaction between the quinonemethide and 2-methylpropene. Both compounds were subjected to a catalytic acidic treatment leading to 2,2-dimethyl-2*H*-chromene. Starting from various salicylaldehydes, the scope of this method was investigated.

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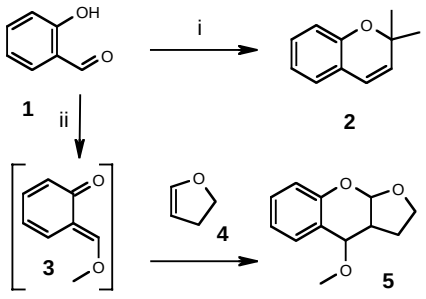
In the course of synthesis of biologically active chromene derivatives, [1] our attention was drawn [2] to a patent [3] reporting a simple preparation of 2,2-dimethyl-2*H*-chromene (**2**) using a reaction between salicylaldehyde (**1**) and 2-methylpropene catalysed by acidic silica-alumina catalysts at 150 °C or zinc chloride at 75°C. More recently [4], the preparation of furo[2,3-*b*]benzopyran **5** was achieved in excellent yield using the ytterbium triflate-catalysed reaction between salicylaldehyde (**1**), trimethylorthoformate and dihydrofuran **4**. As illustrated in Scheme 1, this reaction is an example [5-11] of a [2+4] cycloaddition between the intermediate *o*-quinonemethide **3** and, in the present case, compound **4**. Moreover, a 20% yield preparation of chromene **2** was reported from the reaction between salicylaldehyde diethyl acetal and 2-methylpropene in the presence of borontrifluoride etherate [12].

Scheme 1



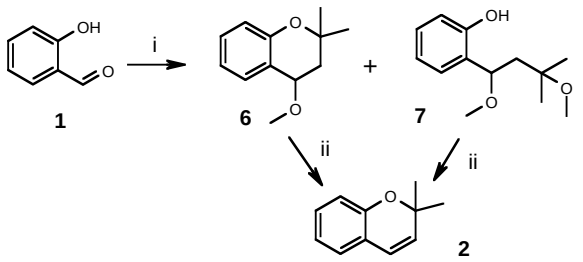
i: 2-methylpropene, silica-alumina catalyst, 150 °C or $ZnCl_2$, 75 °C, 6 h.
ii: $Yb(OTf)_3$, $HC(OMe)_3$, CH_2Cl_2, 25 °C, 12h.

We wish to report here the synthesis of various 2,2-dimethylchromenes *via* an ytterbium triflate-catalysed reaction between salicylaldehydes, trimethylorthoformate and 2-methylpropene.

From the overnight reaction between salicylaldehyde (**1**), trimethylorthoformate, 2-methylpropene and ytterbium triflate in a sealed flask at room temperature, we could isolate and characterise compounds **6** and **7** in 27 and 14% yield respectively. In a control experiment, compound **6** was subjected to the reaction conditions but no ring opening into **7** took place. Moreover, from salicylaldehyde (**1**), no reaction was seen if trimethylorthoformate was omitted. From the results of these negative control experiments, we suggest that compound **7** occurs *via* a reaction related to a carbonyl-ene reaction between the *o*-quinonemethide intermediate **3** and 2-methylpropene followed by a methanol addition on the resulting double bond. Carbonyl-ene reactions catalysed by lanthanide triflate have been reported [13,14] and an example of a competition between this reaction and a Diels-Alder cycloaddition was also observed [13]. An excellent review describes all the reactions that can be catalysed by lanthanides triflates [15]. As related intramolecular cycloadditions have been reported previously [9], including an iodine-catalysed example [10], we also tried iodine on our substrates but without success. In order to obtain the corresponding chromene, compounds **6** and **7** were heated to reflux in toluene in the presence of a catalytic amount of *p*-toluenesulfonic acid (PTSA). It is noteworthy that allowing the resulting methanol to distil from the reaction mixture from time to time was necessary to obtain a complete

conversion of either compounds **6** or **7** into 2,2-dimethylchromene (**2**).

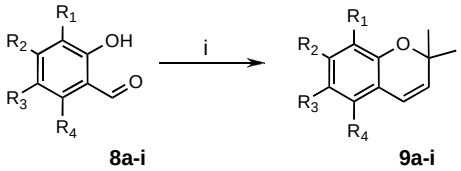
Scheme 2



i: 2-methylpropene, $Yb(OTf)_3$, $HC(OMe)_3$, CH_2Cl_2, 25 °C, 12 h. ii: PTSA, toluene, reflux, 1h.

Using an optimised two steps procedure (a 60 hours-long reaction for the first step), without characterising the intermediate cycloadducts or the corresponding acyclic derivatives, we applied this method to salicylaldehydes **1** and **8a-i** and, depending on the starting material, obtained 2,2-dimethylchromenes as reported in Scheme 3.

Scheme 3



	R1	R2	R3	R4	yield
1	H	H	H	H	42%
8a	H	H	Br	H	67%
8b	H	H	I	H	64%
8c	H	H	NO_2	H	64%
8d	H	H	H	OMe	0%
8e	H	OMe	H	H	0%
8f	H	H	OMe	H	59%
8g	H	Me	H	Me	53%
8h	H	H	OH	H	ni
8i	OH	H	H	H	ni

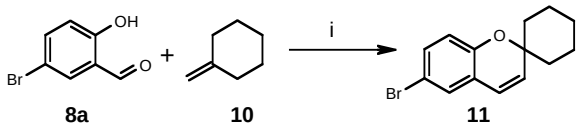
i: 2-methylpropene, $Yb(OTf)_3$, $HC(OMe)_3$, CH_2Cl_2, 25 °C, 60 h. then PTSA, toluene, reflux, 1h. ni: not fully isolated.

From salicylaldehyde **1**, the chromene **2** was isolated in a 42% yield only, probably because of its volatility. On the other hand, the less volatile chromenes **9a**-**c** and **9f**-**g** were obtained in a better yield. A steric hindrance of the aldehyde function of **8d** could explain the lack of occurrence of chromene **9d**, but not the extensive decomposition observed. Moreover, as the methoxy-bearing salicylaldehyde **8e** also led to extensive decomposition, we suggest that a demethylation takes place upon the Lewis acid aldehyde activation thus leading to a *para*-quinonemethide prone to undergo other reactions such as polymerisations [16,17]. A related demethylation could also take place with compound **8d** and the resulting unsaturated β-ketone is likely to undergo many types of side reactions also. Such concerted demethylation cannot be written in the case of the salicyl-aldehyde **8f** and we obtained the corresponding chromene **9f** in acceptable yield. A similar phenomenon was reported for salicylaldehyde **8d** (but not for **8e**) in a related intramolecular study in which *p*-tolunenesulfonic acid was used [9]. We also undertook trials with the hydroxy-bearing aldehydes **8h-i**. However, although the corresponding chromenes **9h-i** could be detected [18] in ^{1}H NMR spectra of sample of the reaction mixture in 10-20% yield, the occurrence of other unidentified compounds of similar polarity has so far prevented a proper purification.

One of the most used methods to prepare chromenes [2] is to build the pyran ring *via* an alkylation of the corresponding phenol with 3-chloro-3-methylbut-1-yne followed by a Claisen rearrangement of the resulting propargyl ether into the target compound [19-21]. If the introduction of a copper-catalysed alkylation method did wonder in yield improvement of this first step [22,23], the following thermal Claisen rearrangement/cyclization is, in some cases, problematic [23,24]. The acid-catalyzed formation of chromenes from few phenols and 3-hydroxy-3-methylbut-1-yne was also reported [25]. A potentially more general method, involves a condensation between phenoxide salts and α,β-unsaturated carbonyl compounds [26]. Remarkably, this reaction also take place between phenols and α,β-unsaturated aldehydes under acid conditions. [27,28] Condensation between salicylaldehydes and unsaturated esters followed by a subsequent decarboxylation was also used [29-31] as well as oxidative cyclization of 2-allylphenols [32,33]. The present work illustrates the versatility of ytterbium triflate and its usefulness in improving the synthetic method mentioned above [3], which required the use of a pressure reactor and heating, into a room temperature experiment only requiring a stoppered glass tube. We hope that the present procedure, in combination with, for example, an *ortho* formylation [34] reaction of the corresponding phenols, will sometime provide a useful alternative for the preparation of benzopyran-containing compounds of biological interest [1,31,35-40]. As a conclusion, we could also prepare, in a rather small 10% yield, the

spirochromene **11** from 5-bromosalicylaldehyde (**8a**) and methylenecyclohexane (**10**).

Scheme 4



i: $Yb(OTf)_3$, $HC(OMe)_3$, CH_2Cl_2, 25 °C, 60h. then p-tolunenesulfonic acid, toluene, reflux, 1h.

Further investigations are in progress in attempt to improve this synthetic access.

EXPERIMENTAL

General Methods.

^1H NMR and ^{13}C NMR spectra were recorded on a Bruker spectrometer at 400 MHz and 100 MHz, respectively. Shifts (δ) are given in ppm with respect to the TMS signal and coupling constants (J) are given in Hertz. Column chromatography were performed over Merck silica gel 60 (0.035 - 0.070 mm), using a solvent pump operating at pressure between 2 and 7 bar (25-50 mL/mn) and an automated collecting system driven by a UV detector set to 254 nm unless stated otherwise. Mass spectra were obtained on an Agilent 1100 serie LC/MSD system using an atmospheric electrospray ionisation system. High resolution mass spectra (HRMS) were obtained by the laboratoire de spectrométrie de masse, CNRS-ICSN, 91198 Gif/Yvette, France.

Isolation of compounds **6** and **7**

In a 60 mL round-bottomed thick glass tube fitted with a PTFE-faced screw-cap, salicylaldehyde (**1**) (1.34 g, 0.011 mol) was dissolved in CH_2Cl_2 (40 mL). Trimethylorthoformate (1.8 mL, 0.016 mol) and ytterbium triflate hydrate (0.34 g, 0.54 mmol) were then added. The resulting solution was cooled to 0°C using an ice bath and 2-methylpropene was bubbled through the solution. The mass added was monitored by periodic weighting and, in the present case, 2.5 g (0.044 mol) of 2-methylpropene was thus added. The glass tube was tightly closed and the solution was stirred at room temperature overnight. The resulting solution was cooled at 0°C prior opening the tube; this was diluted in CH_2Cl_2 and washed three times with a 1 *N* sodium hydrogen carbonate solution. The organic layer was dried over sodium sulfate and concentrated to dryness. The residue was purified by a chromatography over silica gel eluting with a mixture of cyclohexane/CH_2Cl_2 varying from 3/2 to pure CH_2Cl_2. Concentration of the chromatographic fraction gave compound **6** and **7** as described below.

4-Methoxy-2,2-dimethylchroman (**6**).

A pure fraction (0.58 g, 27%) was obtained as an oil. ^1H (400 MHz, $CDCl_3$; data previously reported in CCl_4 [32]): δ = 1.3 (s, 3H); 1.46 (s,3H); 1.98 (dd, 1H, J = 7.5 Hz and 13.5 Hz); 2.12 (dd, 1H, J = 13.5 Hz and 2.4 Hz); 3.49 (s, 3H); 4.46 (m, 1H); 6.79 (dd, 1H, J = 1.0 Hz and 8.2 Hz); 6.93 (m, 1H); 7.19 (m, 1H); 7.40 (m, 1H). ^{13}C (100 MHz, $CDCl_3$): δ = 27.2; 28.8; 37.8; 56.2; 72.4; 75.3; 117.6; 120.4; 122.3; 129.0; 129.6; 153.9. A HRMS spectrum could not be obtained as this compound readily eliminates methanol to give the ion corresponding to chromene (*m/z* = 161).

2-(1,3-Dimethoxy-3-methylbutyl)phenol (**7**).

A fraction (0.36 g, 14%) was obtained as an oil. ^1H (400 MHz, $CDCl_3$): δ = 1.17 (s, 3H); 1.26 (s,3H); 1.89 (dd, 1H, J = 3.0 Hz and 15.1 Hz); 2.14 (dd, 1H, J = 15.1 Hz and 7.7 Hz); 3.23 (s, 3H); 3.36 (s, 3H); 4.53 (dd, 1H, J = 3.0 Hz and 7.7 Hz); 6.89 (m, 2H); 7.07 (dd, 1H, J = 1.7 Hz and 7.3 Hz); 7.18 (m, 1H); 7.90 (s, 1H). ^{13}C (100 MHz, $CDCl_3$): δ = 22.1; 26.0; 47.5; 49.7; 57.4; 74.9; 80.8; 117.3; 120.3; 127.4; 127.6; 129.1; 155.4. *HRMS-FAB*: m/z $[M+Na]^+$ Calcd. for $C_{13}H_{20}O_3Na$: 247.1310. Found: 247,1290.

Representative Procedure for the Synthesis of the 2,2-Dimethyl-2*H*-chromenes, Preparation of Compound **2**.

In a 60 mL round-bottomed thick glass tube fitted with a PTFE-faced screw-cap, salicylaldehyde (**1**) (1 g, 0.0082 mol) was dissolved in CH_2Cl_2 (40 mL). Trimethylorthoformate (1.57 mL, 0.012 mol) and ytterbium triflate hydrate (0.25 g, 0.4 mmol) were then added. The resulting solution was cooled to 0°C using an ice bath and 2-methylpropene was bubbled through the solution. The mass added was monitored by periodic weighting and between 2 and 4 equivalents of 2-methylpropene was thus added. The glass tube was tightly closed and the solution was stirred at room temperature for 60 hours. The resulting solution was cooled at 0°C this was diluted in CH_2Cl_2 and washed three times with a 1 *N* sodium hydrogen carbonate solution. The organic layer was dried over sodium sulfate and concentrated to dryness. The residue was dissolved in toluene (60 mL) and *p*-toluenesulfonic acid (0.03 g, 0.15 mmol) was added. This was heated to reflux for one hour while allowing the methanol to distil from the reaction mixture by removing the water condenser four times (we suggest the much safer use of a distillation apparatus for larger reaction scale). After concentration to dryness, the residue was purified by a chromatography over silica gel to yield the 2,2-dimethyl-2*H*-chromenes as described below.

2,2-Dimethyl-2*H*-chromene (**2**).

Obtained as an oil (42%) eluting with a mixture of cyclohexane/ CH_2Cl_2 9-1. ^1H ($CDCl_3$) and ^{13}C ($CDCl_3$) identical with reported data [23].

6-Bromo-2,2-dimethyl-2*H*-chromene (**9a**).

Obtained as an oil (67%) eluting with a mixture of cyclohexane/ CH_2Cl_2 6-4. ^1H ($CDCl_3$) and ^{13}C ($CDCl_3$) identical with reported data [23].

6-Iodo-2,2-dimethyl-2*H*-chromene (**9b**).

Obtained as an oil (64%) eluting with a mixture of cyclohexane/ CH_2Cl_2 5-5. ^1H ($CDCl_3$) and ^{13}C ($CDCl_3$) identical with reported data [23].

6-Nitro-2,2-dimethyl-2*H*-chromene (**9c**).

The methanol elimination of the intermediate compound was very slow in refluxing toluene and was better achieved neat in the presence of catalytic amount of TSA at 150 °C for 3 hours. The resulting chromene was obtained as a solid (64%; m.p. =

69°C) eluting with a mixture of cyclohexane/ CH_2Cl_2 1-1. ^1H ($CDCl_3$) and ^{13}C ($CDCl_3$) identical with reported data [23].

6-Methoxy-2,2-dimethyl-2*H*-chromene (**9f**).

Obtained as an oil (59%) eluting with a mixture of cyclohexane/ CH_2Cl_2 1-1. ^1H ($CDCl_3$) and ^{13}C ($CDCl_3$) identical with reported data [23].

2,2,5,7-Tetramethyl-2*H*-chromene (**9g**).

Obtained from salicylaldehyde **8g** [41] as an oil (53%) eluting with a mixture of cyclohexane/CH_2Cl_2 9/1. ^1H ($CDCl_3$) and ^{13}C ($CDCl_3$) identical with reported data [27].

6-Bromospiro[chromene-2,1'-cyclohexane] (**11**).

This compound was prepared under the same reaction conditions described above, using 1.5 equivalent of methylene-cyclohexane instead of 2-methylpropene and isolated as an oil (10%) after a chromatography eluting with cyclohexane. ^1H (400 MHz, $CDCl_3$): δ = 1.3-1.56 (m, 1H); 1.5-1.6 (m, 5H); 1.74 (m, 2H); 1.9 (m, 2H); 5.69 (d, 1H, J = 9.8 Hz); 6.28 (d, 1H, J = 9.8 Hz); 6.72 (dd, 1H, J = 0.4 Hz and 8.3 Hz); 7.11 (d, 1H, J = 2.4 Hz); 7.19 (ddd, 1H, J = 0.4 Hz, 2.4 Hz and 8.3 Hz). ^{13}C (100 MHz, $CDCl_3$): δ = 21.7; 25.6; 32.3; 77.6; 113.0; 118.6; 122.1; 124.4; 129.1; 131.8; 132.2; 152.3. *HRMS-FAB*: m/z $[M+H]^+$ Calcd. for $C_{14}H_{16}O^{79}Br$: 279.0385. Found: 279.0380. Calcd. for $C_{14}H_{16}O^{81}Br$: 281.0364. Found: 281.0360.

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REFERENCES

[1] S. Prado, H. Ledeit, S. Michel, M. Koch, J.C. Darbord, S.T. Cole, F. Tillequin and P. Brodin, *Bioorg. Med. Chem.*, **14**, 5423 (2006).

[2] E. E. Schweizer and D. Meeder-Nycz, Chromenes, Chromanones, and Chromones. In *The Chemistry of Heterocyclic Compounds*; Ellis, G.P. Ed John Wiley & Sons: 1977; 31, p 49.

[3] J. T. Arrigo Polycyclic Heterocyclic Compounds. US 2,987,525, 1961.

[4] J. S. Yadav, B. V. S. Reddy, M. Aruna, C. Venugopal, T. Ramalingam, S. K. Kumar and A. C. Kunwar, *J. Chem. Soc. Perkin. Trans. I*, 165 (2002).

[5] J. Brugidou and H. Christol, *C. R. Hebd. Seances Acad. Sci.*, **256**, 3323 (1963).

[6] O. L. Chapman and C. L. McIntosh, *Chem. Commun.*, 383 (1971).

[7] J. P. Marino and S. L. Dax, *J. Org. Chem.*, **49**, 3671 (1984).

[8] Y. Génisson, P. C. Tyler and R. N. Young, *J. Am. Chem. Soc.*, **116**, 759 (1994).

[9] H. Miyazaki, K. Honda, M. Asami and S. Inoue, *J. Org. Chem.*, **64**, 9507 (1999).

[10] J. S. Yadav, B. V. S. Reddy, C. V. Rao and K. V. Rao, *J. Chem. Soc. Perkin. Trans. I*, 1401 (2002).

[11] M. Ashram, D. O. Miller and P. E. Georghiou, *J. Chem. Soc. Perkin. Trans. I*, 1470 (2002).

[12] R. Merten and G. Müller, *Chem. Ber.*, **97**, 682 (1964).

[13] C. Qian and T. Huang, *Tetrahedron Lett.*, **38**, 6721 (1997).

[14] V. K. Aggarwal, G. P. Vennall, P. N. Davey and C. Newman, *Tetrahedron Lett.*, **39**, 1997 (1998).

[15] S. Kobayashi, M. Sugiura, H. Kitagawa and W. W.-L. Lam, *Chem. Rev.*, **102**, 2227 (2002).

[16] R. Gompper, *The Chemistry of Quinonoid Compounds*. ed.; Wiley: New York, 1974; part 2, p 1145.

[17] R. W. Van De Water and T. R. R. Pettus, *Tetrahedron*, **58**, 5367 (2002).

[18] B. A. Chauder, A. V. Kalinin and V. Snieckus, *Synthesis*, 140 (2001).

[19] I. Iwai and J. Ide, *Chem. Pharm. Bull.*, **10**, 926 (1963).

[20] I. Iwai and J. Ide, *Chem. Pharm. Bull.*, **11**, 1042 (1963).

[21] J. Hlubucek, E. Ritchie and W. C. Taylor, *Aust. J. Chem.*, **24**, 2347 (1971).

[22] J. D. Godfrey, R. H. Mueller, T. C. Sedergran, N. Soundararajan and V. J. Colandrea, *Tetrahedron Lett.*, **35**, 6405 (1994).

[23] D. Bell, M.R. Davies, G. Green and I. S. Mann, *Synthesis*, 707 (1995).

[24] J. M. Evans, C. S. Fake, T. C. Hamilton, R. H. Poyser and E. A. Watts, *J. Med. Chem.*, **26**, 1582 (1983).

[25] G. P. Kalena, A. Jain and A. Banerji, *Molecules*, **2**, 100 (1997).

[26] G. Sartori, G. Casiraghi, L. Bolzoni and G. Casnati, *J. Org. Chem.*, **44**, 803 (1979).

[27] B. A. Chauder, C. C. Lopes, R. S. C. Lopes, A. J. M. da Silva and V. Snieckus, *Synthesis*, 279 (1998).

[28] S. L. MacNeil, B. J. Wilson and V. Snieckus, *Org. Lett.*, **8**, 1133 (2006).

[29] Y. Kawase, S. Yamaguchi, H. Horita, J. Takeno and H. Kameyama, *Bull. Chem. Soc. Jpn.*, **55**, 1153 (1982).

[30] S. Yamaguchi, T. Saitoh, M. Kamiumezawa, H. Enomoto and Y. Kawase, *J. Heterocyclic. Chem.*, **29**, 755 (1992).

[31] S. Yamaguchi, M. Nedachi, M. Maekawa, Y. Murayama, M. Miyazawa and Y. Hirai, *J. Heterocyclic. Chem.*, **43**, 29 (2006).

[32] T. Hosokawa, S. Yamashita, S.-I. Murahashi and A. Sonoda, *Bull. Chem. Soc. Jpn.*, **49**, 3662 (1976).

[33] K. C. Nicolaou, J. A. Pfefferkorn, A. J. Roecker, G. Q. Cao, S. Barluenga and S. A. Mitchell, *J. Am. Chem. Soc.*, **122**, 9939 (2000).

[34] T. Suresh, T. Dhanabal, R. N. Kumar and P. S. Mohan, *Heterocyclic Commun.*, **11**, 79 (2005).

[35] V. Kumar, J. Reisch and A. Wickramasinghe, *Aust. J. Chem.*, **42**, 1375 (1989).

[36] J. Razafimbelo, G. Baudouin, F. Tillequin, P. Renard, S. Leonce, A. Pierre and G. Atassi, *Chem. Pharm. Bull.*, **46**, 34 (1998).

[37] N. Costes, H. Le Deit, S. Michel, F. Tillequin, M. Koch, B. Pfeiffer, P. Renard, S. Leonce, N. Guilbaud, L. Kraus-Berthier, A. Pierre and G. Atassi, *J. Med. Chem.*, **43**, 2395 (2000).

[38] H. D. Thi Mai, T. Gaslonde, S. Michel, F. Tillequin, M. Koch, J. B. Bongui, A. Elomri, E. Seguin, B. Pfeiffer, P. Renard, M. H. David-Cordonnier, W. Laine, C. Bailly, L. Kraus-Berthier, S. Leonce, J. A. Hickman and A. Pierre, *J. Med. Chem.*, **46**, 3072 (2004).

[39] V. A. Ashwood, R. E. Buckingham, F. Cassidy, J. M. Evans, E. A. Faruk, T. C. Hamilton, D. J. Nash, G. Stemp and K. Willcocks, *J. Med. Chem.*, **29**, 2194 (1986).

[40] R. Bergmann and R. Gericke, *J. Med. Chem.*, **33**, 492 (1990).

[41] K. v Auwers and E. Borsche, *Chem. Ber.*, 1698 (1915).