Thieme Chemistry Journal Awardees – Where Are They Now? Microwave-Assisted Rhodium-Catalyzed Decarbonylation of Functionalized 3-Formyl-2*H*-chromenes: A Sequence for Functionalized Chromenes like Deoxycordiachromene

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Abstract: 3-Formyl-2*H*-chromenes which are readily accessible through an oxa-Michael reaction of salicylaldehydes and α,β-unsaturated aldehydes undergo a smooth decarbonylation reaction upon treatment with rhodium catalysts. With our method, a great variety of functionalized chromenes is accessible in a two-step sequence from salicylaldehydes.

Key words: domino oxa-Michael–aldol reaction, decarbonylation, benzopyran, rhodium-catalysis, natural products

Chromenes (benzopyrans) form an important class of natural products widespread in higher plants, many of them showing biological activity (Figure 1).[1]

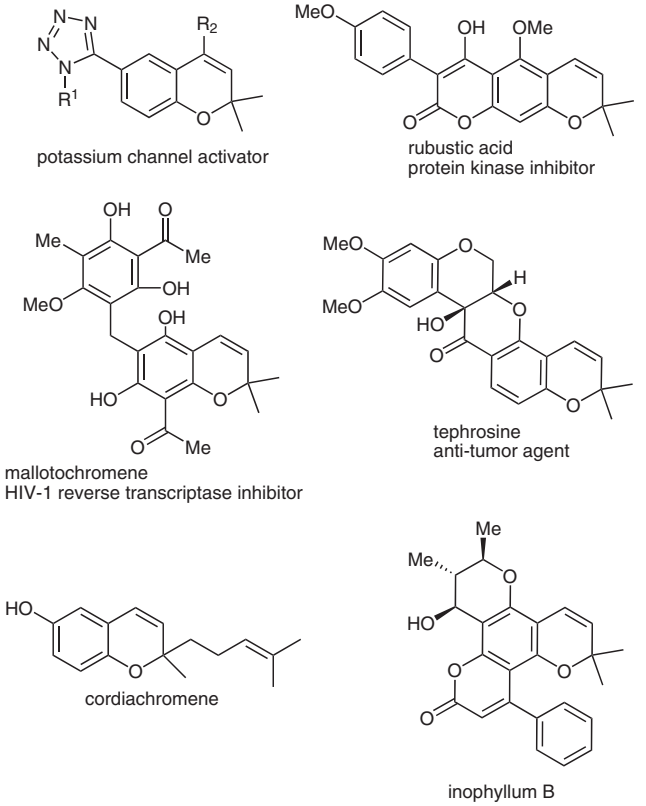

Figure 1 Selected natural products containing a chromene motif

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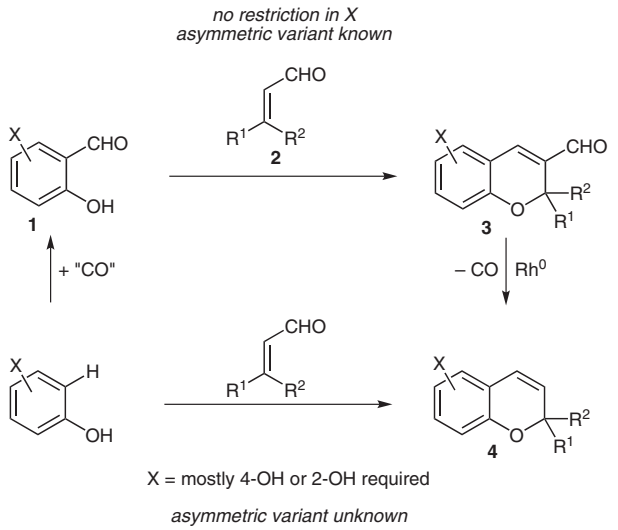
Stefan Bräse was born in Kiel, Germany in 1967. After he studied in Göttingen (Germany), Bangor (UK), and Marseille (France), he received his PhD in 1995, after working with Armin de Meijere in Göttingen. After post-doctoral appointments at Uppsala University in Sweden (Jan E. Bäckvall) and The Scripps Research Institute, La Jolla, USA (K. C. Nicolaou), he began his independent research career at the RWTH Aachen, Germany, in 1997 (associated to Dieter Enders). In 2001, he finished his Habilitation and moved to the University of Bonn as Professor for Organic Chemistry. Since 2003, he is full professor at the University of Karlsruhe, Germany. He is recipient of, among other awards, the OrChem award of the GDCh and the Lilly award. His research interests include methods in drug discovery (including drug delivery), combinatorial chemistry towards the synthesis of biologically active compounds, total synthesis of natural products, and nanotechnology.

Chromenes are also intermediates in the synthesis of many natural products including cannabinoids, anthocyanides, and flavones. Simple hydrogenation of the double bond makes accessible a further substance class, the chromanes.

In principle, chromenes are accessible for example via reaction of propargyl alcohols and ether,[2] Claisen and other rearrangements,[3] and ring-closing-metathesis reactions.[4] In particular, the condensation of α,β-unsaturated aldehydes with resorcylates provides a straightforward access to chromenes.[5] However, differently substituted chromenes cannot be synthesized using this route. We[6] and others[7] have shown that salicylaldehydes and α,β-unsaturated aldehydes provide 3-formyl-2*H*-chromenes in good to excellent yields. Recently, also asymmetric approaches were published.[8]

Herein we report the first synthesis of chromenes from 3-formyl-2*H*-chromenes using a rhodium-catalyzed decarbonylation reaction (Scheme 1).



Scheme 1 Strategies for the synthesis of chromenes based on α,β-

The rhodium-catalyzed decarbonylation reaction has been extensively studied for aromatic and aliphatic compounds,[9] whereas formylalkenes are less frequent being explored (e.g. cinnamal aldehyde).[9d] To our knowledge, this reaction has not been explored for formylchromenes.

As a model system, we synthesized formylchromene **3a** (Table 1, entry 1) by base-catalyzed condensation of salicylaldehyde and citral (54% yield). Catalytic deformylation of the aldehyde **3a** with $RhCl_3$ and dppp in refluxing diglyme yielded deoxycordiachromene **4a** in 59% yield, which was reported before, albeit via a longer sequence.[10]

Then we investigated the scope of the reaction sequence, starting with different substituted salicylaldehydes **1** and α,β-unsaturated aldehydes **2** (Scheme 2). Decarbonylation of the formylchromenes **3** under the standard conditions gave the corresponding chromenes **4** in good yields (Table 1).[11,12]

Table 1 Rhodium-Catalyzed Decarbonylation of Aldehydes[a]

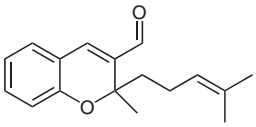
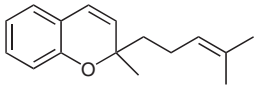
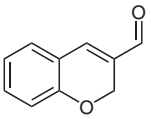
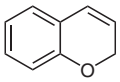
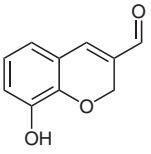
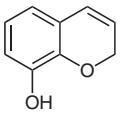
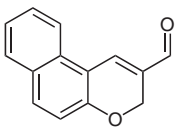
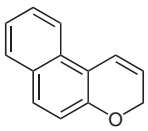
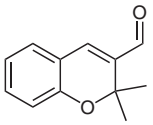
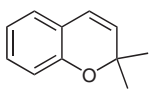
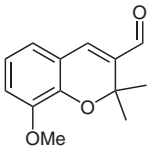
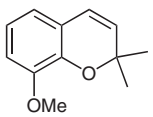
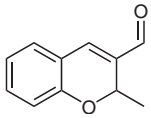
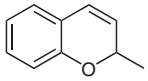
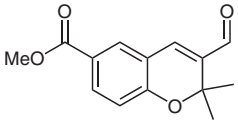
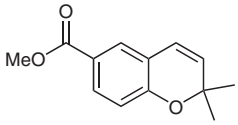
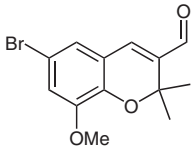
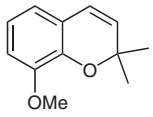
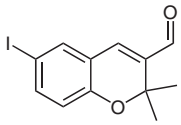
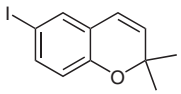
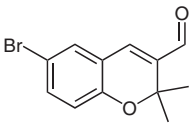
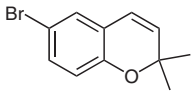
Entry	Aldehyde **3**	Product **4**	Yield (%)
1	 **3a**	 **4a**	59
2	 **3b**	 **4b**	52
3	 **3c**	 **4c**	34
4	 **3d**	 **4d**	52
5	 **3e**	 **4e**	34
6	 **3f**	 **4f**	32

Table 1 Rhodium-Catalyzed Decarbonylation of Aldehydes[a] (continued)

Entry	Aldehyde **3**	Product **4**	Yield (%)
7	 **3g**	 **4g**	39
8	 **3h**	 **4h**	72
9	 **3i**	 **4i**	50
10	 **3j**	 **4j**	–[b]
11	 **3k**	 **4k**	12[c]

[a] Conditions: $RhCl_3 \cdot xH_2O$ (5 mol%), dppp (10 mol%), diglyme, reflux (oil bath), 16 h.
[b] Starting material **3i** (100%) was recovered.
[c] Dehalogenated product was isolated in 9% yield.

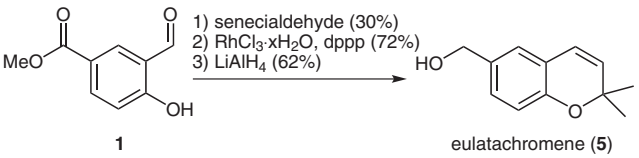
This reaction is compatible with double bonds, hydroxy, methoxy, and ester groups, but not with halides. In the case of aldehyde **3i** a dehalogenation was observed. Aldehyde **3j** could not be converted at all. However, the starting material was recovered quantitatively. As a positive result, we were able to isolate halogenated chromene **4k**, albeit in poor yield.

Due to the moderate yields and the problem of dehalogenation, we investigated alternative reaction conditions.

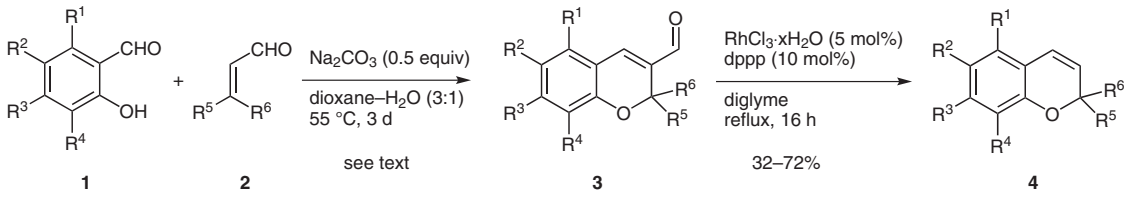
By using microwave irradiation, we could increase the yield of the reaction significantly (Table 2). Furthermore dehalogenation of **4k** was avoided (Table 2, entry 8).

The reduction of chromene **4h** gave eulatachromene (**5**), a natural product isolated from the Italian *Eutypa* culture (Scheme 3).[13]

However, when using enantiopure formylchromene **3g**, synthesized according to reference 8b, the deformylated product **4g** was isolated as a racemate. The racemization took place upon heating in diglyme, regardless of the presence of catalyst, and was complete within six hours. The same racemization occurred under microwave conditions. We suppose an electrocyclic ring-opening–ring-closing



Scheme 3 Synthesis of eulatachromene (**5**): rhodium-catalyzed decarbonylation as a key step

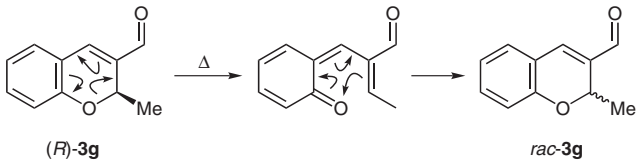


Scheme 2 Rhodium-catalyzed decarbonylation reactions of 3-formyl-2*H*-chromenes **3**

Table 2 Optimization of the Reaction Conditions

Entry	Product **4**	Conditions[a]	Time	Yield (%)
1	**4e**	A	16 h	34
2	**4e**	B	30 min	29
3	**4e**	B	50 min	40
4	**4e**	B	2 × 40 min	60
5	**4a**	A	16 h	59
6	**4a**	B	2 × 40 min	61
7	**4k**	A	16 h	12
8	**4k**	B	30 min	64
9	**4g**	C	4 d	–
10	**4g**	D	60 min	–

[a] Conditions A: $RhCl_3 \cdot xH_2O$ (5 mol%), dppp (10 mol%), diglyme, reflux (oil bath). Conditions B: $RhCl_3 \times xH_2O$ (5 mol%), dppp (10 mol%), diglyme, microwave irradiation (200 °C, 200 W). Conditions C: $[IrCl(cod)]_2$ (2.5 mol%), Ph_3P (5 mol%), THF, reflux (oil bath). Conditions D: $[IrCl(cod)]_2$ (2.5 mol%), Ph_3P (5 mol%), THF, MW irradiation (100 °C, 200 W).



Scheme 4 Proposed mechanism of the racemization of **3g**

mechanism (Scheme 4). Similar racemizations were reported for a series of 2-aryl-2-methyl-2*H*-chromenes.[14] Attempts to decrease the reaction temperature and/or using other catalysts[15] in order to prevent this racemization reaction were unfruitful, yet (Table 2, entries 9 and 10).

In summary, we present the first metal-catalyzed decarbonylation reaction of 3-formylchromenes and its application in the synthesis of the natural product eulatachromene. The application towards the synthesis of more complex chromenes is under investigation.

Acknowledgment

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References and Notes

(1) Shi, Y.; Shi, M. *Org. Biomol. Chem.* **2007**, 1499; and references cited therein.
(2) (a) Iwai, I.; Ide, J. *Chem. Pharm. Bull.* **1963**, *11*, 1042. (b) Babu, K. S.; Raju, B. C.; Praveen, B.; Kishore, K. H.; Murty, U. S.; Rao, J. M. *Heterocycl. Commun.* **2003**, *9*, 519.
(3) (a) Kahn, P. H.; Cossy, J. *Tetrahedron Lett.* **1999**, *40*, 8113. (b) Inoue, S.; Ikeda, H.; Sato, S.; Horie, K.; Ota, T.; Miyamoto, O.; Sato, K. *J. Org. Chem.* **1987**, *52*, 5495. (c) Nicolaou, K. C.; Pfefferkorn, J. A.; Cao, G.-Q. *Angew. Chem. Int. Ed.* **2000**, *39*, 734. (d) Larock, R. C.; Wei, L.; Hightower, T. R. *Synlett* **1998**, 522.
(4) Chang, S.; Grubbs, R. H. *J. Org. Chem.* **1998**, *63*, 864.
(5) El Sohly, M. A.; Boeren, E. G.; Turner, C. E. *J. Heterocycl. Chem.* **1978**, *15*, 699.
(6) (a) Lesch, B.; Toräng, J.; Vanderheiden, S.; Bräse, S. *Adv. Synth. Catal.* **2005**, *347*, 555. (b) Lesch, B.; Toräng, J.; Nieger, M.; Bräse, S. *Synthesis* **2005**, 1888.
(7) (a) Satoh, Y.; Stanton, J. L.; Hutchison, A. J.; Libby, A. H.; Kowalski, T. J.; Lee, W. H.; White, D. H.; Kimble, E. F. *J. Med. Chem.* **1993**, *36*, 3580. (b) Kaye, P. T.; Nocanda, X. W. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1331. (c) Ibrahem, I.; Sundén, H.; Rios, R.; Zhao, G.-L.; Córdova, A. *CHIMIA* **2007**, *61*, 219.
(8) (a) Govender, T.; Hojabri, L.; Moghaddam, F. M.; Arvidsson, P. I. *Tetrahedron: Asymmetry* **2006**, *17*, 1763. (b) Sundén, H.; Ibrahem, I.; Zhao, G.-L.; Eriksson, L.; Córdova, A. *Chem. Eur. J.* **2007**, *13*, 574. (c) Zu, L.; Wang, J.; Li, H.; Xie, H.; Jiang, W.; Wang, W. *J. Am. Chem. Soc.* **2007**, *129*, 1036.
(9) (a) Ohno, K.; Tsuji, J. *J. Am. Chem. Soc.* **1968**, *90*, 99. (b) Doughty, D. H.; Pignolet, L. H. *J. Am. Chem. Soc.* **1978**, *100*, 7083. (c) Beck, C. M.; Rathmill, S. E.; Park, Y. J.; Chen, J.; Crabtree, R. H.; Liable-Sands, L. M.; Rheingold, A. L. *Organometallics* **1999**, *18*, 5311. (d) Kreis, M.; Palmelund, A.; Bunch, L.; Madsen, R. *Adv. Synth. Catal.* **2006**, *348*, 2148. (e) Taarning, E.; Madsen, R. *Chem. Eur. J.* **2008**, *14*, 5638. (f) Use in total synthesis: Takahashi, T.; Naito, Y.; Tsuji, J. *J. Am. Chem. Soc.* **1981**, *103*, 5261. (g) Asymmetric variant: Fessard, T.; Andrews, S. P.; Motoyoshi, H.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 9331. (h) For a review, see: Necas, D.; Kotora, M. *Curr. Org. Chem.* **2007**, *11*, 1566.
(10) (a) Yus, M.; Foubelo, F.; Ferrández, J. V. *Eur. J. Org. Chem.* **2001**, 2809. (b) Asymmetric variants: Bouzbouz, S.; Goujon, J.-Y.; Deplanne, J.; Kirschleger, B. *Eur. J. Org. Chem.* **2000**, 3223.
(11) **Typical Procedure for the Rh-Catalyzed Deformylation of 3-Formyl-2*H*-chromenes**
Formylchromene **3a** (390 μmol), $RhCl_3 \cdot xH_2O$ (19.5 μmol, 5 mol%), and dppp (39.0 μmol, 10 mol%) in diglyme (2 mL) were refluxed under argon for 16 h. After cooling, pentane (10 mL) was added, and the mixture was washed with H_2O (5 × 5 mL). The organic layer was dried over Na_2SO_4 and evaporated. The crude product was purified by column chromatography on SiO_2.
(12) **Selected Data**
Compound **4a**: ^1H NMR (400 MHz, $CDCl_3$): δ = 1.40 (s, 3 H), 1.58 (s, 3 H), 1.60–1.79 (m, 2 H), 1.67 (s, 3 H), 2.12 (m_c, 2 H), 5.11 (tt, *J* = 7.2, 1.4 Hz, 1 H), 5.56 (d, J_{cis} = 9.8 Hz, 1 H), 6.36 (d, J_{cis} = 9.8 Hz, 1 H), 6.77 (d, *J* = 8.0 Hz, 1 H), 6.82 (ddd, *J* = 7.6, 7.4, 1.2 Hz, 1 H), 6.96 (dd, *J* = 7.6, 1.6 Hz, 1 H), 7.09 (ddd, *J* = 8.0, 7.4, 1.6 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.6, 22.7, 25.7, 26.5, 41.3, 78.4, 116.1, 120.5, 121.1, 122.8, 124.1, 126.3, 129.0, 129.6, 131.7, 153.2. MS–FAB: *m/z* (%) = 229.2 (11) [M^+ + H], 228.2 (18) [M^+], 145.1 (100) [$M^+ - C_6H_{11}$], 136.1 (10). HRMS: *m/z* calcd for $C_{16}H_{20}O$: 228.1514. Found: 228.1510. Anal. Calcd for $C_{16}H_{20}O$: C, 84.16; H, 8.83. Found: C, 84.14; H, 8.69.
(13) Smith, L. R.; Mahoney, N.; Molyneux, R. J. *J. Nat. Prod.* **2003**, *66*, 169.
(14) Harié, G.; Samat, A.; Guglielmetti, R.; Van Parys, I.; Saeyens, W.; De Keukeleire, D.; Lorenz, K.; Mannschreck, A. *Helv. Chim. Acta* **1997**, *80*, 1122.
(15) Iwai, T.; Fujihara, T.; Tsuji, Y. *Chem. Commun.* **2008**, 6215.