Tetrahedron Letters 52 (2011) 3926–3928

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

# ReCl(CO)$_5$-catalyzed cyclocondensation of phenols with 2-methyl-3-butyn-2-ol to afford 2,2-dimethyl-2*H*-chromenes

Hanxiang Zeng[a], Jia Ju[a], Ruimao Hua[a,b,*]

[a] *Department of Chemistry, Tsinghua University, Key Laboratory of Organic Optoelectronics & Molecular Engineering of Ministry of Education, Beijing 100084, China*
[b] *State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, China*

ARTICLE INFO

*Article history:*
Received 31 March 2011
Revised 16 May 2011
Accepted 20 May 2011
Available online 27 May 2011

*Keywords:*
Condensation
2,2-Dimethyl-2*H*-chromenes
2-Methyl-3-butyn-2-ol
Phenol
Rhenium

## ABSTRACT

A direct one-pot route for the synthesis of 2,2-dimethyl-2*H*-chromenes by Re(CO)$_5$Cl-catalyzed cyclocondensation of phenols with 2-methyl-3-butyn-2-ol has been developed. The easy availability of starting materials, mild reaction conditions, high atom-efficiency, and the use of a recoverable catalyst are advantages of this procedure.

2,2-Dimethyl-2*H*-chromenes (2,2-dimethyl-2*H*-1-benzopyran) structures can be found as parent molecules in a wide variety of important natural products.[1] 2,2-Dimethyl-2*H*-chromenes have also been well applied as important intermediates to synthesize numerous pharmaceutical and biologically active compounds.[2] Therefore, a number of synthetic methods have been developed for the construction of 2,2-dimethyl-2*H*-chromenes, most notably the condensation of metal phenoxides with α,β-unsaturated carbonyl compounds,[3] dehydration of chromanols in the presence of acidic compounds,[4] condensation of l,l-diethoxy-3-methyl-2-butene with phenols catalyzed by pyridine,[5] condensation of phenols with 3-methyl-2-butenal either mediated by phenylboronic acid,[6] catalyzed by ethylenediamine diacetate,[7] or catalyzed by base under microwave irradiation,[8] ytterbium triflate-catalyzed reaction of salicylaldehydes, trimethylorthoformate and 2-methylpropene,[9] and photocyclization of 3-aryl-l,l-dimethylprop-2-en-l-ol.[10] Despite extensive studies into synthetic preparations of 2,2-dimethyl-2*H*-chromenes as described above, developing a general strategy with high atom-efficiency which uses easily accessible starting materials under mild conditions is still of interest. Therefore, in continuation of our interest in the synthesis of *O*-heterocyclic compounds using alkynes as a reaction partner,[11] and the application of low-valence rhenium compounds as catalysts in organic transformations[12] in this work we have investigated the reaction of phenols with 2-methyl-3-butyn-2-ol in the presence of rhenium compounds to give 2,2-dimethyl-2*H*-chromenes.[13]

The reaction of 4-methoxyphenol (**1a**) with 2-methyl-3-butyn-2-ol (**2a**) was first studied to optimize the cyclocondensation conditions (Table 1). When a mixture of **1a** (1.0 mmol), **2a** (3.0 mmol) and ReBr(CO)$_5$ (0.1–0.03 mmol) in toluene (1.5 mL) was heated in a sealed tube in air atmosphere with stirring at 130 °C for 24 h, the GC and GC–MS analyses of the reaction mixtures showed that **2a** was consumed completely, and the desired cycloadduct 6-methoxy-2,2-dimethyl-2*H*-chromene (**3a**) was formed in moderate GC yields (67–56%, entries 1–4). Decreasing the reaction temperature to 110 °C resulted in a higher yield of 75% (entry 5 vs entry 1), indicating that a lower reaction temperature could significantly improve the formation of **3a**, likely due to decreasing the rate of side reactions of **2a**. Indeed, when the reaction was repeated at 90 and 60 °C, **3a** was obtained in 78% (entry 6) and 85% GC yields (entry 7), respectively. However, when the reaction temperature was further decreased to room temperature, no reaction occurred (entry 8).

In addition, the achieved yield of **3a** also exhibited a noticeable solvent effect. In CH$_2$Cl$_2$, **3a** was obtained in only 63% yield (entry 9), whereas in *p*-xylene, cyclohexane, octane and hexane, the reaction afforded **3a** in high yields (entries 10–13).

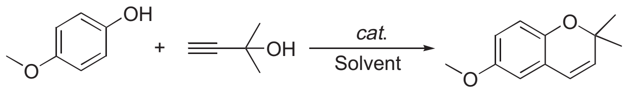
We also examined the catalytic activity of other rhenium complexes (entries 14–17). Although NH$_4$ReO$_4$ and Re$_2$(CO)$_{10}$ did not display catalytic activity, ReCl(CO)$_5$ and CpRe(CO)$_5$ (Cp = cyclopentadienyl) showed high activity, and the highest yield of **3a** (95% GC yield, 90% isolated yield) was obtained by using 7.0 mol % of ReCl(CO)$_5$.

---

* Corresponding author. Fax: +86 10 62771149.
*E-mail address:* ruimao@mail.tsinghua.edu.cn (R. Hua).

0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.05.093

**Table 1**
Reaction of 4-methoxyphenol (**1a**) with 2-methyl-3-butyn-2-ol (**2a**)[a]



**1a** **2a** **3a**

| Entry | Catalyst (mol %) | Solvent | Temp (°C) | Yield[b] (%) |
|---|---|---|---|---|
| 1 | $ReBr(CO)_5$ (10) | Toluene | 130 | 67 |
| 2 | $ReBr(CO)_5$ (7) | Toluene | 130 | 64 |
| 3 | $ReBr(CO)_5$ (5) | Toluene | 130 | 59 |
| 4 | $ReBr(CO)_5$ (3) | Toluene | 130 | 56 |
| 5 | $ReBr(CO)_5$ (7) | Toluene | 110 | 75 |
| 6 | $ReBr(CO)_5$ (7) | Toluene | 90 | 78 |
| 7 | $ReBr(CO)_5$ (7) | Toluene | 60 | 85 |
| 8 | $ReBr(CO)_5$ (7) | Toluene | rt | <5 |
| 9 | $ReBr(CO)_5$ (7) | $CH_2Cl_2$ | 60 | 63 |
| 10 | $ReBr(CO)_5$ (7) | *p*-Xylene | 60 | 86 |
| 11 | $ReBr(CO)_5$ (7) | Cyclohexane | 60 | 80 |
| 12 | $ReBr(CO)_5$ (7) | Octane | 60 | 90 |
| 13 | $ReBr(CO)_5$ (7) | Hexane | 60 | 92 |
| 14 | $ReCl(CO)_5$ (7) | Hexane | 60 | 95(90) |
| 15 | $ReCp(CO)_5$ (7) | Hexane | 60 | 90 |
| 16 | $NH_4ReO_4$ (7) | Hexane | 60 | <5 |
| 17 | $Re_2(CO)_{10}$ (7) | Hexane | 60 | <5 |
| 18 | $[ReCl(CO)_4]_2$ (3) | Hexane | 60 | 96 |

[a] Unless otherwise noted, reactions were carried out using 1.0 mmol of **1a** with 3.0 mmol of 2-methyl-**3**-butyn-2-ol and catalyst in 1.5 mL solvent for 24 h in a sealed tube.
[b] GC yield based on the amount of **1a** used. Number in parenthesis is isolated yield.

It is important to note that a white crystal of $[ReCl(CO)_4]_2$ (67% relative to $ReCl(CO)_5$ employed) was obtained from the reaction mixture of entry 14, when the reaction mixture was cooled to ambient temperature, indicating that the homogeneous rhenium(I) catalyst could be partly recovered after the reaction. The structure of the observed $[ReCl(CO)_4]_2$ was confirmed by X-ray structure analysis.[14] Furthermore, $[ReCl(CO)_4]_2$ might be considered to be the intermediate of the catalytic procedure, since it showed similar catalytic activity to $ReCl(CO)_5$ (entry 18 vs entry 14).

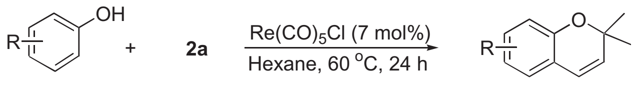
To assess the generality of the given catalytic process, the reactions of a variety of phenols with **2a** under the reaction conditions as indicated in entry 14 of Table 1 were examined. As shown in Table 2, the reaction of *p*-(**1b**), *o*-(**1c**) and *m*-cresol (**1d**) afforded the corresponding 2,2-dimethyl-2*H*-chromenes **3b**, **3c** and **3d** in good isolated yields (entries 1–3). It should be noted that the reaction of **1d** with **2a** produced two regioisomers, from which **3d** was isolated in analytical purity in 68% yield (entry 3). The use of phenol (**1e**) gave a somewhat low yield (55%, entry 4).

Naphthopyrans are an important class of *O*-heterocyclic compounds, which are not only found widely in natural products,[15] but have also been well-studied as photochromic agents.[16] The given catalytic procedure can also be applied to the synthesis of naphthopyrans by the reaction of naphthol with **2a**. For example, the reaction of β-naphthol (**1f**) gave two naphthopyran isomers **3f** and **3f′** which were isolated in 68% and 13% yields, respectively (entry 5). α-Naphthol (**1g**) showed low reactivity under similar reaction conditions to give the expected cycloadduct **3g** in 30% isolated yield (entry 6).

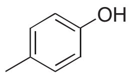
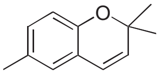
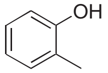
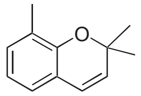
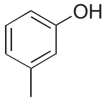
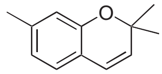
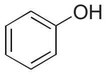
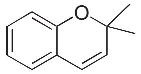
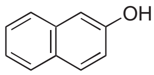
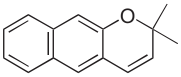
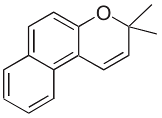
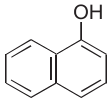
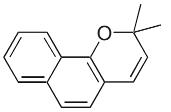
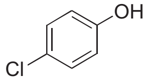
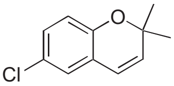
Under the same reaction conditions, phenols bearing an electron-withdrawing group also underwent cycloaddition. For example, 4-chlorophenol (**1h**) reacted with **2a** to afford **3h** in 53% isolated yield (entry 7).

In addition, the reactions of **1a** with 2-phenyl-3-butyn-2-ol (**2b**) (Eq. 1), and with 1-ethynylcyclohexanol (**2c**) (Eq. 2) afforded the expected cycloadducts **3i** and **3j** in 28% and 65% isolated yields, respectively.

**Table 2**
$ReCl(CO)_5$-catalyzed reaction of phenols with 2-methyl-3-butyn-2-ol (**2a**)[a]

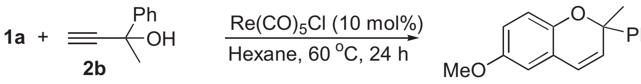


**1** **3**

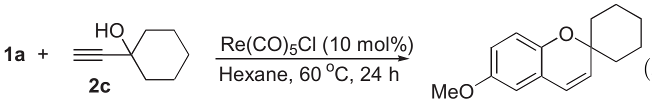
| Entry | Phenol | Product | Yield[b] (%) |
|---|---|---|---|
| 1 |  **1b** |  **3b** | 73 |
| 2 |  **1c** |  **3c** | 62 |
| 3 |  **1d** |  **3d** | 68 |
| 4 |  **1e** |  **3e** | 55 |
| 5 |  **1f** |  **3f** | 68 |
| | |  **3f′** | 13 |
| 6 |  **1g** |  **3g** | 30 |
| 7 |  **1h** |  **3h** | 53 |

[a] Unless otherwise noted, reactions were carried out using 1.0 mmol of phenols, 3.0 mmol of **2a** and 0.07 mmol of $ReCl(CO)_5$ in 1.5 mL hexane.
[b] Isolated yield based on the phenols used.

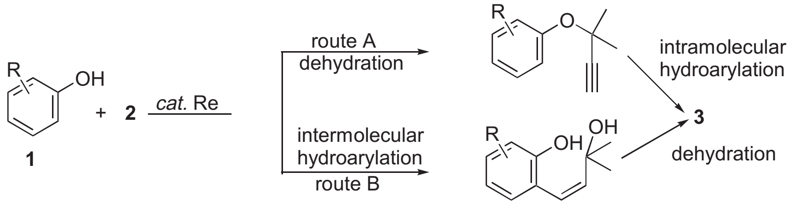
Early transition-metal complexes have found widespread use as transition metal Lewis acid catalysts in diverse organic transformations.[17] In our previous report and other group works, low-valence rhenium complexes were found to be efficient catalysts to catalyze dehydration of alcohols[18] and hydroarylation of alkynes[19] to construct C–O and C–C bonds, respectively. Therefore, two possible routes including a dehydration and hydroarylation are proposed for the condensation, as shown in Scheme 1. However, since the current condensation proceeded with high chemoselectivity and regioselectivity with hydroarylation at the *ortho*-position of the phenols only, route A is considered to be more favorable.



1.5 equiv. **3i** 28% (1)



3.0 equiv. **3j** 65% (2)



**Scheme 1.** Proposed mechanism for rhenium-catalyzed condensation of phenols with propargyl alcohols.

In summary, we have developed rhenium(I)-catalyzed condensation of phenols with 2-methyl-3-butyn-2-ol to afford 2,2-dimethyl-2*H*-chromenes in mild to high yields. This procedure provides a highly atom-efficient route to 2,2-dimethyl-2*H*-chromenes having various substituents on the benzene ring. Mild reaction conditions without a requirement for an inert atmosphere and partial recovery of the rhenium catalyst are notable advantages of the given catalytic procedure.

A typical experimental procedure for $ReCl(CO)_5$-catalyzed cyclocondensation of 4-methoxyphenol (**1a**) with 2-methyl-3-butyn-2-ol (**2a**) affording 6-methoxy-2,2- dimethyl-2*H*-chromene (**3a**) (Table 1, entry 14): A mixture of 4-methoxyphenol (**1a**) (124.0 mg, 1.0 mmol), 2-methyl-3-butyn-2-ol (**2a**) (252.3 mg, 3.0 mmol), $ReCl(CO)_5$ (25.3 mg, 0.07 mmol), and *n*-hexane (1.5 mL) was heated at 60 °C (oil bath temperature) with stirring in a screw-capped thick-walled Pyrex tube in air atmosphere, with the mixture becoming homogeneous within few minutes of heating. After heating for 6 h, the reaction mixture was cooled to room temperature, diluted with $CH_2Cl_2$ (4.0 mL), and then *n*-octadecane (92.5 mg, 0.36 mmol) was added as an internal standard for GC analysis. After GC and GC–MS analyses of the reaction mixture, volatiles were removed under reduced pressure, and the residue was subjected to preparative TLC isolation (silica gel, eluted with a solvent mixture of $CH_2Cl_2$ and petroleum ether (1:4)) to afford **3a** as a pale yellow oil (171.1 mg, 0.9 mmol, 90%). The GC analysis of the reaction mixture revealed the formation of **3a** in 95% GC yield. Data for **3a**: pale yellow oil; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 6.64–6.45 (m, 3H), 6.19 (d, 1H, $J = 9.6$ Hz), 5.54 (d, 1H, $J = 9.6$ Hz), 3.65 (s, 3H), 1.32 (s, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 153.9, 146.8, 131.8, 122.5, 122.0, 116.9, 114.3, 111.6, 75.8, 55.8, 27.7; GC–MS $m/z$ (% rel. inten.) 190 ($M^+$, 20), 175 (100), 160 (5), 132 (13), 124 (6), 77 (4).

## Acknowledgment

This project was supported by the National Natural Science Foundation of China (20972084 and 21032004).

## Supplementary data

Supplementary data (general method, characterization data, charts of $^1$H, $^{13}$C NMR for all products and the full X-ray diffraction data for $[Re(CO)_4Cl]_2$) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.05.093.

## References and notes

1. Selected reports, see: (a) Nicolaou, K. C.; Pfefferkorn, J. A.; Cao, G.-Q. *Angew. Chem., Int. Ed.* **2000**, *39*, 734–739; (b) Nicolaou, K. C.; Pfefferkorn, J. A.; Roecker, A. J.; Cao, G.-Q.; Barluenga, S.; Mitchell, H. J. *J. Am. Chem. Soc.* **2000**, *122*, 9939–9953.
2. Selected reports, see: (a) Mannhold, R.; Cruciani, G.; Weber, H.; Lemoine, H.; Derix, A.; Weichel, C.; Clementi, M. *J. Med. Chem.* **1999**, *42*, 981–991; (b) Sant'Anna, S. S.; Evangelista, E. A.; Alves, R. B.; Raslan, D. S. *Chem. Nat. Compd.* **2005**, *41*, 385–387; (c) Page, P. C. B.; Buckley, B. R.; Heaney, H.; Blacker, A. J. *Org. Lett.* **2005**, *7*, 375–377; (d) Szczepanik, M.; Obara, R.; Szumny, A.; Gabrys, B.; Halarewicz-Pacan, A.; Nawrot, J.; Wawrzenczyk, C. *J. Agric. Food Chem.* **2005**, *53*, 5905–5910.
3. Sartori, G.; Casiraghi, G.; Bolzoni, L.; Casnati, G. *J. Org. Chem.* **1979**, *44*, 803–805.
4. (a) Bergmann, R.; Gericke, R. *J. Med. Chem.* **1990**, *33*, 492–504; (b) Kureshy, R. I.; Ahmad, I.; Pathak, K.; Khan, N. H.; Abdi, S. H. R.; Jasra, R. V. *Catal. Commun.* **2009**, *10*, 572–575.
5. North, J. T.; Kronenthal, D. R.; Pullockaran, A. J.; Real, S. D.; Chen, H. Y. *J. Org. Chem.* **1995**, *60*, 3397–3400.
6. Chauder, B. A.; Lopes, C. C.; Lopes, R. S. C.; da Silva, A. J. M.; Snieckus, V. *Synthesis* **1998**, 279–282.
7. Lee, Y. R.; Choi, J. H.; Yoon, S. H. *Tetrahedron Lett.* **2005**, *46*, 7539–7543.
8. Subburaj, K.; Trivedi, G. K. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 259–263.
9. Prado, S.; Janin, Y. L.; Bost, P.-E. *J. Heterocycl. Chem.* **2006**, *43*, 1605–1608.
10. Pandey, G.; Krishna, A. *J. Org. Chem.* **1988**, *53*, 2364–2365.
11. (a) Hua, R.; Tanaka, M. *New J. Chem.* **2001**, *25*, 179–184; (b) Huang, Q.; Hua, R. *Catal. Commun.* **2007**, *8*, 1031–1035; (c) Zhao, W.-G.; Hua, R. *Tetrahedron* **2007**, *63*, 11803–11808; (d) Li, M.; Hua, R. *J. Org. Chem.* **2008**, *73*, 8658–8660.
12. Hua, R.; Jiang, J.-L. *Curr. Org. Synth.* **2007**, *4*, 151–174.
13. The similar cyclocondensation of phenols with propargyl alcohols to afford substituted 2*H*-chromenes, see: (a) Ishino, Y.; Mihara, M.; Hayakawa, N.; Miyata, T.; Kaneko, Y.; Miyata, T. *Synth. Commun.* **2001**, *31*, 439–448; (b) Coelho, P. J.; Salvador, M. A.; Heron, B. M.; Carvalho, L. M. *Tetrahedron* **2005**, *61*, 11730–11743; (c) Zhao, W.; Carreira, E. M. *Org. Lett.* **2006**, *8*, 99–102; (d) Moorthy, J. N.; Koner, A. L.; Samanta, S.; Roy, A.; Nau, W. M. *Chem. Eur. J.* **2009**, *15*, 4289–4300.
14. CCDC818106 contains supplementary crystallographic data of $[Re(CO)_4Cl]_2$ for this Letter. These data can be obtained free of charge via www.ccdc.cam.ac.uk.
15. (a) Singh, I. P.; Bharate, S. B.; Bhutani, K. K. *Curr. Sci.* **2005**, *89*, 269–290; (b) Lee, Y. R.; Kim, Y. M. *Helv. Chim. Acta* **2007**, *90*, 2401–2413.
16. (a) Tanaka, K.; Aoki, H.; Hosomi, H.; Ohba, S. *Org. Lett.* **2000**, *2*, 2133–2134; (b) Gartner, C. A.; Wen, B.; Wan, J.; Becker, R. S.; Jones, G.; Gygi, S. P.; Nelson, S. D. *Biochemistry* **2005**, *44*, 1846–1855; (c) Rawat, M.; Prutyanov, V.; Wulff, W. D. *J. Am. Chem. Soc.* **2006**, *128*, 11044–11053.
17. For transition metal-based Lewis acids, see: (a) Beck, W.; Sünkel, K. *Chem. Rev.* **1988**, *88*, 1405–1421; (b) Murahashi, S. I.; Takaya, H. *Acc. Chem. Res.* **2000**, *33*, 225–233.
18. Liu, Y.; Hua, R.; Sun, H.-B.; Qiu, X. *Organometallics* **2005**, *24*, 2819–2821.
19. Kuninobu, Y.; Kikuchi, K.; Tokunaga, Y.; Nishina, Y.; Takai, K. *Tetrahedron* **2008**, *64*, 5974–5981.