

SYNTHESIS OF SUBSTITUTED FLAVONES AND ARYLCHROMONES USING P AND Si KEGGIN HETEROPOLYACIDS AS CATALYSTS

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Abstract : A simple and clean procedure for the preparation of functionalized flavones and chromones using commercial Keggin heteropolyacid in acetonitrile medium is described for the cyclization of 1-(2-hydroxyaryl)-3-aryl-1,3-propanodiones. Sixteen examples are reported, yields ranging in 60-91%; five substituted 2-naphthylchromones are prepared for the first time.

Introduction

Compounds containing the chromone skeleton (4*H*-benzopyran-4-one) are widely distributed in the plant kingdom; they constitute a group of compounds in the flavonoid family (1). These compounds have multiple biological properties, for example anti-inflammatory, antibacterial, antitumor (2), antioxidant (3), anti HIV (4), vasodilator, antiviral, antiallergic (5) and neuroprotective. Some flavonoids inhibit the histamine release from human basophils and rat mast cells (6). Moreover, it is known that some flavonoids have antifeedant activity against some phytophagous insects and a *Coptotermes* sp. subterranean termite (7, 8).

The importance of flavones and their derivatives has led to the development of various methods for their synthesis; for example the Kostanecki-Robinson strategy (9a), from chalcones (9b), or via the Baker-Venkataraman rearrangement to 1,3-diaryl 1,3-diketones (9c, 10). The latter compounds give 2-arylchromones on cyclocondensation. Different media have been employed for performing it, for example using excess of sulfuric acid in glacial acetic acid (11, 12); cationic exchange resins in isopropanol (13) glacial acetic acid-anhydrous sodium acetate or aqueous potassium carbonate (14). Greener procedures have been recently described, for example using CuCl₂ in ethanol and microwave irradiation (2).

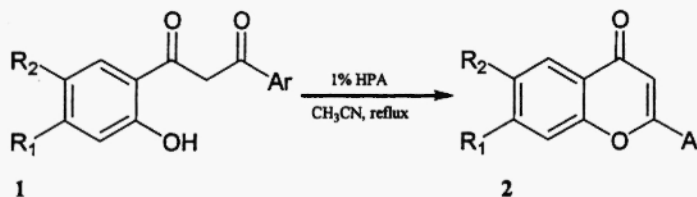
Environmental pollution is a usual drawback caused from the use of common acid catalysts like sulfuric, phosphoric, hydrofluoric acids, or boron trifluoride; frequently corrosion problems appear (15). Nevertheless, it is possible avoid them by using an insoluble acid, for example a heteropolyacid (HPA) as catalyst. HPAs are useful solid catalysts because of their superacidic properties (16); catalysis by HPAs or some of their derivatives is a field of increasing importance worldwide. There is a great activity in basic research as well as in developing of technological processes involving them (17-19). Varied reactions are currently catalyzed by HPAs, being important dehydration (20), cyclization (15), esterification (21), amine oxidation and olefin epoxidation (22). HPAs are widely applicable in production of fine chemicals (23). Heteropolycompounds with Keggin-type primary structure are polynuclear complexes mainly composed by Mo, W or V as polyatoms (M) and P, Si or Ge as central atoms (X). The Keggin structure involves a central tetrahedron XO₄ surrounded by 12 octahedra MO₆. Keggin catalysts could be either multi-electron oxidants or strong acids, with an acid strength higher than that of the classical mineral acids. These properties can be controlled by a proper choice of the heteroatom and polyatoms (15).

Experimental

All the yields were calculated from crystallized products. All the products were identified by comparison of analytical data (mp, IR, NMR, TLC) with those reported or with authentic samples prepared by the conventional method, using sulfuric acid as the catalyst. Both the commercial catalysts MPA (molybdophosphoric acid, $H_3PMo_{12}O_{40} \cdot n H_2O$, Merck) and MSA (molybdosilicic acid, $H_3SiMo_{12}O_{40} \cdot n H_2O$, Aldrich) were heated at 100° for 4 hours previously to be used in the experiments. All the starting β -diketones **1a-p** were prepared following a procedure described elsewhere (24). Characterization of the products was made by 1H NMR (400.1 MHz) and ^{13}C NMR (100.6 MHz), using a Bruker Avance DPX-400 spectrometer at room temperature. The chemical shift standard was internal tetramethylsilane. Signal assignments were assisted by APT (attached-proton test), DEPT, gs-COSY, gs-HMQC, and gs-HMBC experiments using standard Bruker software.

Typical Procedure for 2-substituted chromones: 0.5 mmol of β -diketone (see Scheme 1 and Table 1) and bulk HPA catalyst (1% mmol) were dissolved in 2.5 ml acetonitrile. The mixture was refluxed with stirring for 3 h. The reaction mixture was concentrated in vacuum and extracted with dichloromethane; the catalyst was filtered and washed twice with dichloromethane. The extracts were combined and washed with NaOH 3M; then, they were dried with anhydrous sodium sulfate and concentrated in vacuum. Sometimes, flash chromatography on silica was necessary to complete the isolation. All the solid crude products were recrystallized from methanol or hexanes.

Scheme 1. Baker-Venkataraman synthesis of flavones and substituted chromones.

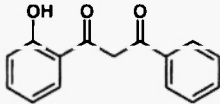
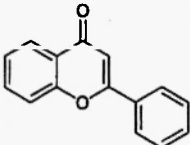
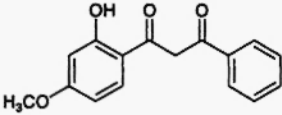
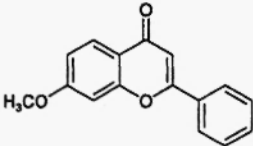
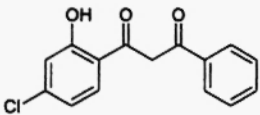
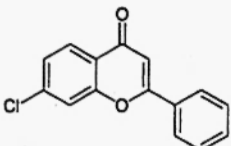
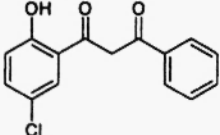
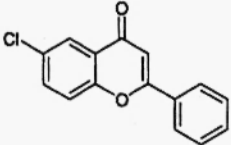
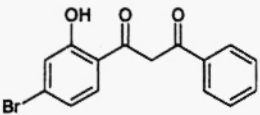
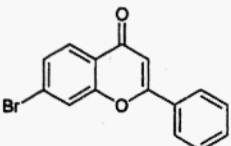
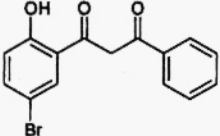
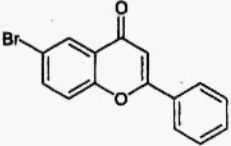
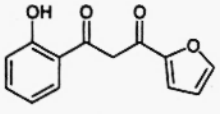
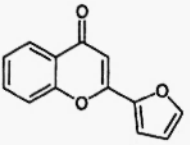
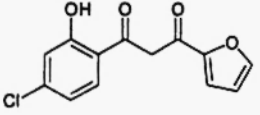
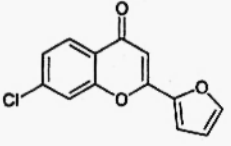
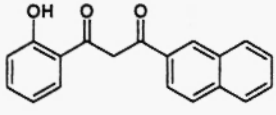
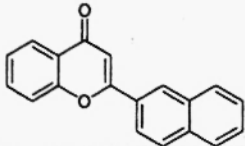


Ar = Phenyl, Furyl, 1-Naphthyl, 2-Naphthyl
 R_1 = H, CH_3 , OCH_3 , F, Cl, Br
 R_2 = H, Br, Cl, NO_2

Results

In this paper we report the catalytic activity of two Keggin-type HPAs: molybdophosphoric acid (MPA) and molybdosilicic acid (MSA), in a sustainable preparation of substituted flavones, 2-furylchromones and 2-naphtylchromones from 1-(2-hydroxyphenyl)-3-aryl-1,3-propanediones (see Scheme 1). The obtained results are shown in Table 1. The experiments were carried out in refluxing acetonitrile, in the presence of 1% (mole) catalyst, till consumption of the β -diketone or until no changes in the composition of the reaction mixture were observed. The use of just 1% mmol of HPAs is enough to push the reaction forward; higher amounts of the catalyst did not improve the results. Products **2k-2m**, **2o**, **2p** are novel; as an example, NMR characterization for **2m** is included below.

Table-1: Synthesis of flavones, furylchromones and naphthylchromones using molybdophosphoric acid (MPA) and molybdosilic acid (MSA) as catalysts.

Entry	Diketone 1	Flavone/Chromone 2	% yield 2 (MPA) ^a	% yield 2 (MSA) ^b
a			87 (86, 86) ^c	85
b			91	-
c			82	60
d			80	72
e			78	71
f			78	64
g			86	66
h			70	-
i			88	82

(Continued overleaf)

Table-1 (Continued) : Synthesis of flavones...

Entry	Diketone 1	Flavone/Chromone 2	% yield 2 (MPA) ^a	% yield 2 (MSA) ^b
j			91	63
k			88	76
l			77	-
m			80	-
n			81	-
o			81	73
p			78	69

^a Using 1% bulk MPA as catalyst. ^b Using 1% bulk MSA as catalyst. ^c Yields of the immediate first and second reutilization.

7-Chloro-2-(1-naphthyl)-4H-benzopyran-4-one (**2m**): m.p. 198-199°C, ¹H NMR (CDCl₃, 400 MHz): δ 8.56 (1H, d, J= 8.27, H-5), 8.12-8.14 (1H, m, H-8'), 8.06 (1H, d, J= 8.16, H-4'), 7.97-7.99 (1H, m, H-5'), 7.78 (1H, dd, J= 7.16, J= 1.12, H-2'), 7.56-7.63 (4H, m, H-8, H-3', H-6', H-7'), 7.46 (1H, dd, J= 8.52, J= 1.88, H-6), 6.70 (1H, s, H-3). ¹³C NMR (CDCl₃, 100 MHz): 177.4 (C-4), 165.6 (C-2), 156.8 (C-9), 139.9 (C-7), 133.7 (C-8a'), 131.7 (C-4'), 130.3 (C-4a'), 130.2 (C-1'), 128.8 (C-2'), 128.0 (C-5'), 127.6 (C-8'), 127.2 (C-7'), 126.7 (C-5), 126.2 (C-6), 125.1 (C-6'), 124.7 (C-3'), 122.5 (C-10), 118.3 (C-8), 113.3 (C-3).

Discussion

In all the cases, the desired products (flavones, 2-naphthylchromones or 2-furylchromones) were obtained with high selectivity, almost free of secondary products. The unchanged starting materials were recovered nearly quantitative. Recycling of the catalyst MPA (Table 1, entry 1) was checked in two consecutive batches after the first use; the catalyst showed almost constant activity. The yields obtained using MPA were higher than those involving MSA, probably because the acidity of MPA is higher than that of MSA (25). Due to the difference in the yields, some examples were carried out using only MPA catalyst. No stereoelectronic effects owing to the substituent were observed over the yield, for each of the catalysts. Yields of flavones were similar to those of furylchromones and naphthylchromones (see Table 1). However, the nitro-substituted diketone 1-(2-hydroxy-5-nitrophenyl)-3-phenyl-1,3-propanodione failed to give the expected flavone after 16 hr at 81°C.

Conclusions

The described procedure provides a clean and useful alternative for preparing flavones, 2-furylchromones and 2-naphthylchromones. The activity of the catalyst, practically constant in consecutive reaction batches, and their high recovery play for both low environmental impact and low cost. Other "green" advantages of the procedure are the low generation of waste and the replacement of corrosive soluble mineral acids.

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References

1. S. Martens and A. Mithöfer, *Phytochemistry* **66**, 2399 (2005).
2. G. Kabalka and A. Mereddy, *Tetrahedron Lett.* **46**, 6315 (2005) and references cited therein.
3. J. Grassmann, S. Hippeli, and E. Eltsner, *Plant Physiol. Biochem.* **40**, 471 (2002).
4. J. Wu, X. Wang, Y. Yic and K. Leeb, *Bioorg. Med. Chem. Lett.* **13**, 1813 (2003).
5. J. Seijas, M. Vázquez-Tato and R. Carballido-Reboredo, *J. Org. Chem.* **70**, 2855 (2005) and references cited therein.
6. S. Yano, H. Tachibana and K. Yamada, *J. Agric. Food Chem.* **53**, 1812 (2005).
7. M. Morimoto, K. Tanimoto, S. Nakano, T. Ozaki, A. Nakano and K. Komai, *J. Agric. Food Chem.* **51**, 389 (2003).
8. W. Ohmura, S. Doi, M. Aoyama and S. Ohara, *J. Wood Sci.* **46**, 149 (2000).
9. J. Staunton, Gamma-Pyrone and Chromones in D. Barton and W. D. Ollis (Eds.), *Comprehensive Organic Chemistry. The Synthesis and Reactions of Organic Compounds*, Vol. 4. Pergamon Press, Oxford, 1979. (a) pp. 678-679. (b) pp. 687-688. (c) pp. 678.
10. A. Ganguly, S. Kaur, P. Mahata, D. Biswas, B. Pramanik and T. Chan, *Tetrahedron Lett.* **46**, 4119 (2005) and references cited therein.
11. R. Varma, R. Saini and D. Kumar, *J. Chem. Research (S)* **348** (1998) and references cited therein.
12. T. S. Wheeler, *Org. Synth.* **32**, 72 (1952).
13. Y. Hoshino and N. Takeno, *Bull. Chem. Soc. Japan* **60**, 1919 (1987).
14. S. Saxena, J.K. Makrandi and S. Grover, *Synthesis* **697** (1985).
15. P. Vázquez, L. Pizzio, G.P. Romanelli, J.C. Autino, C. Cáceres and M. Blanco, *Appl. Catal. A: Gen.* **235**, 233 (2002).
16. I. Kozhevnikov, *Chem. Rev.* **98**, 171 (1998).
17. M. Misono, *Korean J. Chem. Eng.* **14**, 427 (1997).
18. Z. Zhao, Z. Li, G. Wang, W. Qiao and L. Cheng, *Prog. Chem.* **16**, 620 (2004).
19. G. Yadav, *Catal. Surv. Asia* **9**, 117 (2005).
20. W. Turek, J. Haber and A. Krowiak, *Appl. Surf. Sci.* **252**, 823 (2005).
21. L. Pizzio, P. Vázquez, C. Cáceres and M. Blanco, *Appl. Catal. A: Gen.* **256**, 125 (2003).
22. Y. Ding, B. Ma, Q. Gao, G. Li, L. Yan and J. Suo, *J. Mol. Catal. A: Chem.* **230**, 121 (2005).
23. For example (a) D. Brunel, A. Blanc, A. Galarneau and F. Fajula, *Catal. Today* **73**, 139 (2002). (b) G.P. Romanelli, D. Bennardi, D.M. Ruiz, G. Baronetti, H.J. Thomas and J.C. Autino, *Tetrahedron Lett.* **45**, 8935 (2004). (c) A.S. Dias, M. Pillinger and A.A. Valente, *Appl. Catal. A: General* **285**, 126 (2005). (d) F.F. Bamoharram, M.M. Heravi, M. Roshani, A. Gharib and M. Jahangir, *J. Mol. Catal. A: Chemical* **252**, 90 (2006).
24. J.L. Jios, J.C. Autino and A.B. Pomilio, *An. Asoc. Quím. Argent.* **83**, 183 (1995).
25. M. Timofeeva, *Appl. Catal. A: Gen.* **256**, 19 (2003).

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