

Silica gel supported InBr_3 and InCl_3 : new catalysts for the facile and rapid oxidation of 2'-hydroxychalcones and flavanones to their corresponding flavones under solvent free conditions

Naseem Ahmed, Hasrat Ali and Johan E. van Lier*

Department of Nuclear Medicine and Radiobiology, Faculty of Medicine, Université de Sherbrooke, Sherbrooke, Que, Canada J1H 5N4

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Abstract—Silica gel supported InBr_3 or InCl_3 (15–20 mol%) were explored as a new solid-support catalysts for the facile and efficient oxidation, under solvent free conditions, of 2'-hydroxychalcones and flavanones to yield the corresponding flavones in >80% yield. The catalysts are easily prepared, stable, and efficient under mild reaction conditions.
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Flavones (also known as 2-phenylchromones), constitute a large number of natural products with many medicinal applications.¹ Because of their broad range of biological activities,² this class of molecules has been extensively investigated and more than 4000 chemically unique flavonoids have been isolated from plants.³ Recently, particular attention has been focused on the protective biochemical action of naturally occurring antioxidants and on their mechanism of action. The phenolic compounds (e.g., flavones) are considered to play an important role in the prevention of oxidative damage in living systems.⁴ Moreover, in capturing free radicals, their antioxidant activity is highly influenced by the presence of oxygenated groups (e.g., hydroxy and methoxy) on the aromatic rings. A large number of flavonoids are known to exhibit binding affinity and anti proliferate effects against breast cancer cells in culture. Previously, we have reported a number of ^{18}F -labeled estrogen derivatives as possible agents for PET imaging of breast cancer.⁵ While evaluating the ^{18}F -labeling of flavone analogs, we explored methods for the oxidation of 2'-hydroxychalcones and flavanones to their corresponding flavones, which led to the current observations.

Among various methods,^{6a} flavones have been synthesized by the oxidation of 2'-hydroxychalcones and flavanones. Reagents that have been used for this purpose are SeO_2 -pentan-1-ol,^{6c} Pd-C/vacuum ,⁷ I_2 -DMSO,⁸ SeO_2 -DMSO,⁹ DDQ-dioxane,¹⁰ NaIO_4 -DMSO,¹¹ nickel peroxide-dioxane,¹² H_2O_2 -NaOH,¹³ Dowex-2-propanol,¹⁴ SeO_2 -dioxane,¹⁵ SeO_2 -*iso*-amyl alcohol,¹⁶ Br_2 -NaOH,¹⁷ $\text{Ti}(\text{NO}_3)_3 \cdot 3\text{H}_2\text{O}$,¹⁸ and I_2 -triethylene glycol.¹⁹ Most of these methods are of limited use⁶ since yields are low and mixtures of products, containing flavones, flavonones, and aurones are obtained.^{10,12} Furthermore these procedures require prolonged reaction times and high temperatures.^{11,19} Other limitations concern 2'-hydroxychalcones possessing a phloroglucinol oxygenation pattern in ring A.^{8,9} In the later case a complex mixture was obtained lacking the desired products. Recently, indium halides have emerged as potential and efficient catalyst over conventional Lewis acids in promoting various organic transformations,^{20,21} which led us to explore these catalysts for the synthesis of flavones.

General procedure for the oxidation of 2'-hydroxychalcones and flavanones: The 2'-hydroxychalcones or flavanones (1.0 mmol, dissolved in a minimum amount of ethyl acetate) are added to silica gel supported InBr_3 (2.0 g, 15–20 mol%)²³ and the solvent is removed. The dry mixture is heated with stirring at 130–140 °C in an inert container for different periods of time (Table 1). The reaction mixture is directly applied on a silica gel column and eluted with a mixture of ethyl acetate–hexane (1:1). Eluting products are characterized as flavones

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* Corresponding author. Tel.: +1 819 564 5409; fax: +1 819 564 5442; e-mail: johan.e.vanlier@usherbrooke.ca

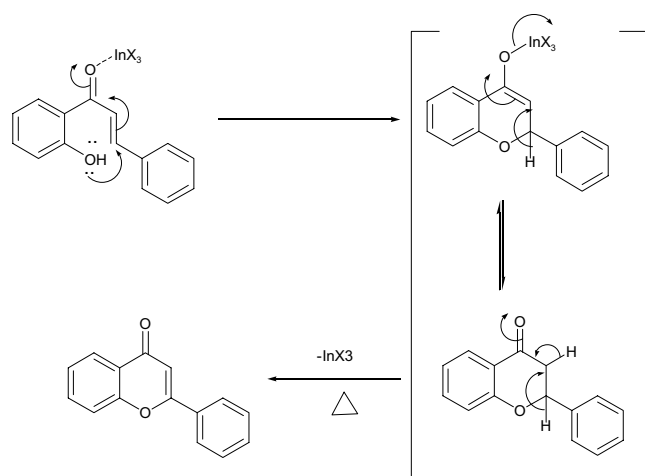
Table 1. Silica gel supported InBr₃ or InCl₃ mediated oxidative cyclization of 2'-hydroxychalcones and flavanones to their flavones

Entry	Substrate	Time (min)	Product	Yield (%) ^{a,b,c}
1		45		96
2		45		98
3		45		95
4		45		86
5		60		85
6		55		90
7		70		82
8		50		92
9		45		95
10		45		80
11		45		90
12		120		75
13		120		65

^a Substrate (1.0mmol), silica gel supported InBr₃ or InCl₃ (2.0g, 15–20mol%) were heated at 130–140°C and stirred for the indicated time.^b Isolated and nonoptimized yield. Conversion based on reactant recovery was 100% except for entries 12 and 13 (75–80%).^c Identification of the products was ascertained by ¹H NMR, ¹³C NMR and mass spectroscopy and compared with Aldrich available spectroscopic data.

based on their spectral properties (^1H NMR, ^{13}C NMR, MS) relative to authentic spectra.²⁴ Using this procedure a number of substituted chalcone and flavanone derivatives were found to give the corresponding flavones. Substituents are well tolerated and the products were obtained in high yield. Using silica gel supported InCl_3 under the above conditions the reaction also proceeds smoothly although overall yields were lower as those obtained with the InBr_3 catalyst. This is in accordance with previous reports on the relative catalytic activities of these indium halides in the absence of silica gel.²⁵ The reactions did not occur in the presence of silica gel alone. Contrary to previously reported methods, this procedure tolerates a wide range of substitutions on the aromatic rings of the substrate (Table 1). Generally, oxidation of substrates with unprotected hydroxyl groups on the aromatic rings were reported to give poor yields.^{1,15,19} However, we found that our new reagent is equally suitable and efficient for the oxidation of such derivatives (entries 5, 7, 13). At lower temperature ($<120^\circ\text{C}$) the crude ^1H NMR spectra of the reaction mixture showed the presence of different products including flavanones, in addition to flavones and starting material (2'-hydroxychalcones). Increasing the reaction time did not result in complete conversion to flavones. This suggests the formation of the flavanone as an intermediate, which would be in line with the high temperature requirement for achieving the activation energy for oxidation/dehydrogenation of the flavanone to the flavone.¹⁹ Interestingly, it has been reported that 2'-hydroxychalcones on silica gel supported BiCl_3 at lower temperature ($60\text{--}70^\circ\text{C}$) provide a constrained environment resulting in formation of the corresponding flavonones.^{22,26} In order to verify the possible role of flavanone as an intermediate during the formation of flavone under our reaction conditions, we used some flavanones as substrates revealing their rapid conversion to the corresponding flavones (entries 12, 13). These data support a reaction pathway for the formation of flavone where the flavanone is a transient intermediate (Scheme 1).

In conclusion, we have shown that flavones can easily be prepared from 2'-hydroxychalcones and flavanones in



Scheme 1.

high yield under solvent free condition using commercially available and inexpensive indium salts and silica gel. The advantages of this procedure over earlier reported processes include its simplicity, fast and clean reactions, high yield, and the use of environmentally friendly catalysts.

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23. Silica gel supported InBr_3 and InCl_3 preparation (15–20 mol%): InBr_3 (60–70 mg) is dissolved in a minimum amount of ethyl acetate, added dropwise to silica gel (1.0 g, 60A, 70–230 mesh, EM Science, Germany) and the slurry is evaporated to dryness at 80 °C. This silica gel supported InBr_3 was kept under argon, and used for 6 months without changing its catalytic activity. InCl_3 (14–19 mg) dissolved in a minimum amount of acetonitrile is added to silica gel (1.0 g), evaporated to dryness as above, and stored under argon for further use.
24. Entry 2, (2', 6'-dichloroflavone), mp 146–148 °C, ^1H NMR (CDCl_3 , 300 MHz): δ 7.48–7.42 (m, 3H), 7.25–7.19 (m, 2H), 7.13 (s, 1H), 6.86 (dd, $J = 8.4, 2.1$ Hz, 1H), 6.65 (dd, $J = 8.4, 2.1$ Hz, 1H). ^{13}C NMR (CDCl_3 , 75.46 MHz): 103.4, 107.9, 114.2, 116.3, 127.8, 128.9, 132.1, 138.6, 144.6, 154.7, 157.8, 164.2, 183.4. EIMS: m/z 292 (M^+) (70%), 257 ($\text{M}-\text{Cl}$) (100%), 222 ($\text{M}-2\text{Cl}$) (25%), 195, 166.
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