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A two step synthesis of BzR/GABAergic active flavones via a Wacker-related oxidation

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ABSTRACT

A general route for the synthesis of biologically important flavones is reported via a two step sequence employing a catalytic Wacker–Cook oxidation[4b] as the key step.

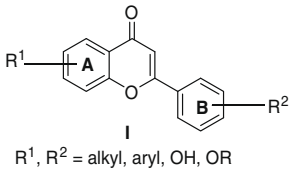
Flavones are a group of natural products which occur as secondary metabolites in plants and exhibit remarkable biological activity (e.g., *anti*-malarial, *anti*-oxidant, *anti*-inflammatory, and insecticidal properties).[1] In addition, the core structure of flavones (Fig. 1) is also found in several natural products rendering this privileged scaffold interesting from a synthetic point of view.[2] Analysis of a recent review indicated flavones bind potently to the benzodiazepine binding site (Bz BS) on γ-aminobutyric acid (A) receptors (GABA-A).[3a] Importantly, Häberlein et al. had reported that the steric orientation of the substituents in flavones must lie in a coplanar fashion to the aromatic ring for potent affinity to BzR.[3d]

In order to search for subtype selective flavones[3a] for BzR simple access to a broad spectrum of these ligands was required. The initial idea for a two step process for the synthesis of various flavones originated from the work of Maldonado et al. who had employed a process they termed, a Wacker–Cook oxidation.[4b] It had been conceived from a one pot synthesis of enones,[4a] which had been developed during the synthesis of the alkaloids (−)-alstonerine and 6-oxoalstophylline, as well as for the synthesis of the isoflavone core structure.[4b]

We wish to report the successful synthesis of a wide variety of flavones via this catalytic approach in a two step process. This new procedure is catalytic in palladium (II) rather than stoichiometric.[2]

The starting enone for this catalytic oxidation was readily prepared via an aldol condensation of the corresponding *o*-hydroxyacetophenone **II** with the required benzaldehyde **III** to give the α,β-unsaturated ketone **IV** following the literature procedure (Scheme 1).[5] Optimization of the oxidation conditions employed in the established method[4b] was carried out in order to reduce the palladium required to a catalytic amount (10 mol %). The α,β-unsaturated ketone **IV** (R^1 = Cl, R^4 = NO_2) was employed as the model compound to optimize the reaction conditions of the intramolecular oxidation for the synthesis of the substituted flavones. Initial attempts by the application of the original Wacker conditions[6a,b] provided very poor conversion of the starting unsaturated ketone to the desired flavones (~20% even after 7 days) as well as the use of stoichiometric amounts of palladium (Table 1, entry 1).[6]

Addition of *t*-BuOOH as the oxidizing agent to the reaction mixture[4a,b] increased the yield but only moderately (Table 1, entry 2). Interestingly, the yield remained constant even when the catalyst loading was reduced or the oxidizing agent was changed to NMO (Table 1, entries 3 and 4). However, better yields were achieved when *t*-BuOOH was used in excess and added portion-wise at 1 h intervals to the reaction vessel. The increase in yield was now maintained even when the amount of palladium was again lowered to 10 mol % (Table 1, entries 7 and 8). A further improvement in yield was realized by the addition of the oxidizing agent



I

R^1, R^2 = alkyl, aryl, OH, OR

Figure 1. General structure of the flavones.

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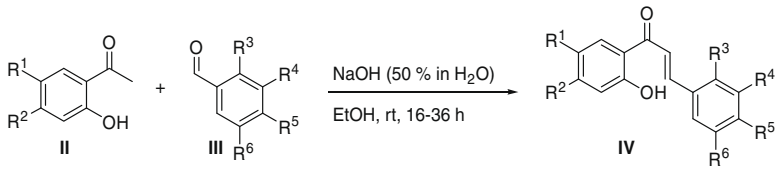
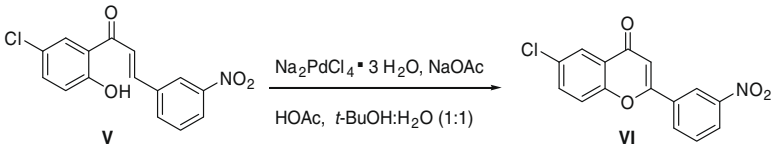


Scheme 1. Synthesis of the starting material for the flavones.

Table 1
Optimization studies of the oxidation process



	Temp. (°C)	Catalyst loading	Oxidizing agent	Yield (%)	Time (h)
1	80	1.3 equiv	—	33	12
2	80	1 equiv	*t*-BuOOH (1.3 equiv)	66	21
3	80	40 mol %	*t*-BuOOH (1.3 equiv)	67	20
4	90	1 equiv	NMO	67	5
5	80	40 mol %	*t*-BuOOH (5 × 1.3 equiv)	74	7
6	70	20 mol %	*t*-BuOOH (5 × 1.3 equiv)	75	8
7	70	10 mol %	*t*-BuOOH (5 × 1.3 equiv)	76	8
8	70	10 mol %	*t*-BuOOH (6 equiv)	85	4
9	70	2 mol %	*t*-BuOOH (6 equiv)	64	16
10	50	10 mol %	*t*-BuOOH (6 equiv)	0	24

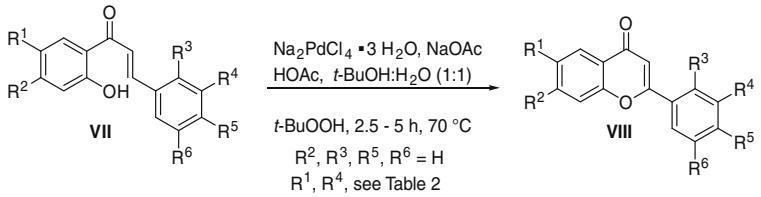
t-BuOOH in excess in one portion at the beginning of the reaction and 10 mol % of the palladium catalyst was employed (Table 1, entry 8). The complete consumption of the starting material was observed and a higher yield of the desired flavone was obtained. In agreement with previous work,[4a,b] as well as with the reports of Tsuji[6c] the palladium (0), so generated, in the catalytic cycle was reoxidized to the active palladium (II) species with *t*-BuOOH before the palladium (0) was converted to the inactive metallic palladium (0). Again as in the earlier work of Tsuji[6c] and others,[4a,b] the key step to form the enone was the palladium hydride elimination set up to generate the flavone core.

Further attempts at a lower catalyst loading or a lower reaction temperature resulted in reduced yields or no conversion of the starting material at all, respectively. It must be pointed out the best solvent ratio and conditions for this oxidation (20 mmol concentration in *t*-BuOH/H_2O (1:1), 10 mol % $Na_2PdCl_4{\cdot}3H_2O$, NaOAc, AcOH, 6 equiv *t*-BuOOH) are different from the classical Wacker or Tsuji–Wacker oxidations (see brief experimental for details).

These newly developed oxidation conditions were applied to the synthesis of a number of flavones of interest in good to excellent yields (Table 2). Depicted in Table 2 are the structures and K_i values of flavones that bound to the benzodiazepine receptor of GABA(A)ergic ion channels previously reported on synaptosomal membranes by Häberlein et al.[3d]

Importantly, no byproduct was observed from the Michael addition to generate the dihydroflavone which is very difficult to convert to a flavone in some cases. This oxidation was successful in the presence of a wide variety of functional groups. Key to the general nature of this oxidation, electron donating groups (EDG) nor electron withdrawing groups (EWG) on both aromatic rings of the starting α,β-unsaturated ketone **IV** had little if any impact on the yields (Table 2).

Table 2
Synthesis of flavones via the oxidation process (I) and K_i values of flavones that bound to BZR/GABAergic receptors



	R^1	R^4	Yield (%)	Time (h)	K_i (nM)[3a]
1	F	NO_2	89	3.5	182
2	Cl	NO_2	85	4	8.0
3	Br	Cl	83	2.5	17.0
4	Cl	Br	84	4.5	23.0
5	Br	Br	87	2.5	19.1
6	NO_2	NO_2	76	4	12.0
7	Br	NO_2	87	3	1.0

To extend the scope of the newly developed oxidation system a broad spectrum of flavone analogues which contained either an EWD or EDG in the **B** ring at various positions were synthesized in excellent yields (Table 3). To date, this approach to substituted flavones in ring **B** has been successful with a variety of substituents. Flavones with ring **B** which contained highly electron rich substituents (Table 3, entries 1, 4, 7, 8 and 10) as well as highly electron poor substituents (Table 3, entries 9, 11, 12 and 13) gave good yields consistently. Even substituents which contained a phenolic group in ring **B** (Table 3, entries 2 and 5) gave good yields in this oxidation without byproduct formation from any intermolecular process.

Finally, depicted in Table 4 is a series of flavones prepared via this strategy with an EDG in ring **A** and with an EDG or EWG in ring **B**.

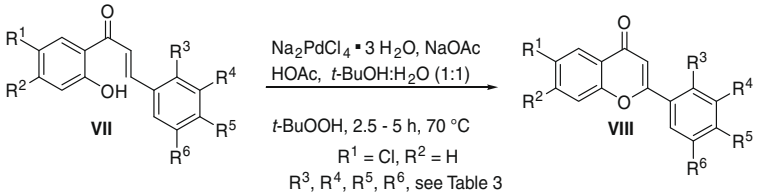
In summary, a catalytic oxidation procedure has been developed for the synthesis of flavones in high yield. This simple two step process provides the first simple entry into a series of flavones with EDG or EWG in ring **A** or **B** at will and should provide a simple route to substituted analogues for SAR studies at BzR.[3a]

Procedure for the preparation of the starting material for the example in Table 3, *entry 4:* To a solution of 4-*t*-butylbenzaldehyde (299 mg, 1.84 mmol, 1.25 equiv) in ethanol (5 mL) at rt was added a solution of aqueous NaOH (50% in H_2O, 3 mL) and 5′-hydroxy-2-chloroacetophenone (250 mg, 1.47 mmol, 1 equiv). The mixture which resulted was stirred after which it turned from a yellowish color to red in a few minutes and was stirred for 18 h at room temperature. After addition of EtOAc/H_2O (1:1, 20 mL), the aqueous layer was extracted with EtOAc (3 × 15 mL) and the combined organic layers were washed with a saturated solution of $NaHCO_{3(aq)}$ until the color of the organic phase changed to yellow and the organic layer was then washed with a saturated solution of $NaCl_{(aq)}$. The organic phase was dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The oily residue was purified by flash column chromatography on silica gel using *n*-hexane/EtOAc (20:1) as the eluent. The α,β-unsaturated ketone was obtained as a yellowish solid in 76% yield (352 mg, 1.12 mmol) present as the *trans*-isomer as the only product, as expected.

R_f: 0.91 on silica gel (*n*-hexane/EtOAc 6:1); mp = 138 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.78 (s, 1H), 7.94 (d, J = 15.4 Hz, 1H), 7.87 (d, J = 2.5 Hz, 1H), 7.61–7.63 (m, 2H), 7.53 (d, J = 15.4 Hz, 1H), 7.47–7.49 (m, 2H), 7.43 (dd, J = 8.8, 2.5 Hz, 1H), 6.98 (d, J = 9.1 Hz, 1H), 1.36 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.8, 162.0, 155.1, 146.5, 136.0, 131.6, 128.8, 128.8, 126.1, 123.4, 120.7, 120.2, 118.5, 35.0, 31.1 ppm; HRMS (ESI) $(M+H)^+$ calcd for $C_{19}H_{20}ClO_2$ 315.1146, found: 315.1140.

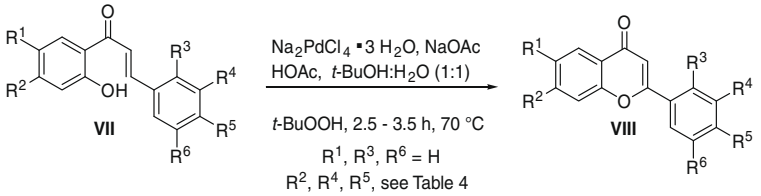
Procedure for the oxidation of ***IV*** *to flavones in* Table 3, *entry 4:* To a mixture of *t*-BuOH/H_2O (1:1, 5 mL) and AcOH (670 μL) were added NaOAc (7.8 mg, 0.095 mmol), the α,β-unsaturated ketone **IV** (30 mg, 0.095 mmol), $Na_2PdCl_4{\cdot}3H_2O$ (10 mol %, 2.3 mg) and *t*-BuOOH (70% in H_2O, 6 equiv). The brownish solution which

Table 3
Synthesis of flavones via the oxidation process (II)



	R^3	R^4	R^5	R^6	Yield (%)	Time (h)
1	H	OMe	H	OMe	84	4.5
2	H	OH	H	H	84	2.5
3	H	OMe	H	H	89	2.5
4	H	H	*t*-Bu	H	97	3
5	H	H	OH	H	79	4
6	H	H	H	H	88	3
7	OMe	H	H	OMe	92	3
8	H	H	OMe	H	90	4
9	H	CF_3	H	H	74	3.5
10	H	H	NMe_2	H	81	5
11	H	H	F	H	72	2.5
12	H	H	CF_3	H	78	5
13	H	H	CN	H	71	3.5

Table 4
Synthesis of flavones via the oxidation process (III)



	R^2	R^4	R^5	Yield (%)	Time (h)
1	OMe	H	F	81	3
2	OMe	NO_2	H	77	3.5
3	OMe	H	OMe	82	2.5
4	OMe	OMe	H	81	3.5

resulted was allowed to warm to 70 °C and stirred for 3 h. The mixture was then cooled to room temperature, after which EtOAc (10 mL) and a saturated solution of $NaHCO_{3(aq)}$ (10 mL) were added carefully. The aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic layers were washed successively with saturated solutions of $NaHCO_{3(aq)}$ and $NaCl_{(aq)}$ after which it was dried ($MgSO_4$). After filtration the solvent was removed under reduced pressure and the solid residue purified by flash column chromatography on silica gel using *n*-hexane/EtOAc (15:1) as the eluent. The flavone was obtained in 97% (29 mg, 0.092 mmol) yield.

R_f: 0.51 on silica gel (*n*-hexane/EtOAc 6:1); mp = 187 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, J = 2.6 Hz, 1H), 7.82–7.85 (m, 2H), 7.62 (dd, J = 9.0, 2.6 Hz, 1H), 7.50–7.56 (m, 3H), 6.80 (s, 1H), 1,37 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.2, 163.9, 155.7, 154.5, 133.8, 131.1, 128.5, 126.2, 126.1, 125.1, 124.9, 119.8, 106.9, 35.1, 31.1 ppm; HRMS (ESI) $(M+H)^+$ calcd for $C_{19}H_{18}ClO_2$ 313.0990, found: 313.0986.

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