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Facile Syntheses of 3-Hydroxyflavones

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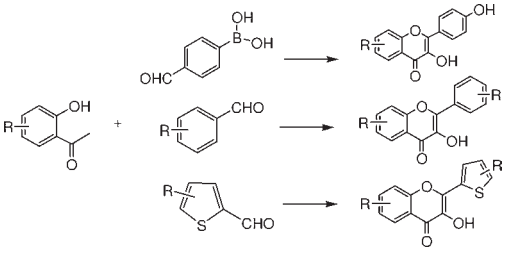
ABSTRACT



Modification of the present synthetic methods led to the syntheses of 3-hydroxyflavones in a shorter reaction time, with simple purification and higher yields. Application of the method provided the syntheses of 3HFs having a hydroxyl group on the phenyl ring (ring B) in one step, which is an improvement compared to the four steps, long reaction time, and low yield using the current method available in the literature.

3-Hydroxyflavones (3HFs) **1** (Figure 1) are a unique class of flavonoids, which are composed of fused phenyl and pyranyl rings (A- and C-rings) and a phenyl moiety (ring B) attached to the ring C. They are mainly found in a wide variety of natural sources and are known to affect various biological processes, including the development of cancer, platelet aggregation, detoxification, and inflammatory and immune responses.[1] Moreover, it has been indicated that a daily intake of flavonoids from fruits and vegetables reduces the risk of coronary heart disease.[2] Among 3HFs, quercetin[3] and kaempferol[4] are the most known natural 3-hydroxyflavones.

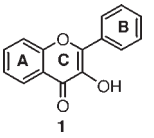


Figure 1. 3-Hydroxyflavone.

In addition to their important biological properties, 3HFs are environmentally sensitive (solvatochromic) fluorescent dyes, which make them attractive for researchers as prospective molecular fluorescent sensors, particularly for monitoring biomolecular interactions.[5] This property comes from their well separated dual emission bands in

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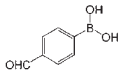
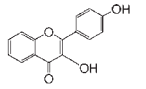
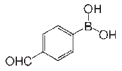
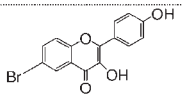
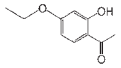
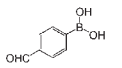
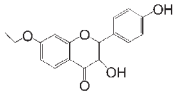
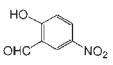
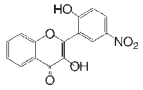
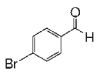
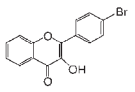
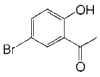
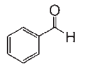
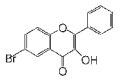
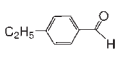
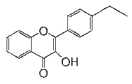
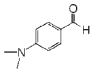
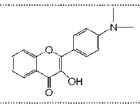
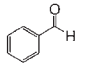
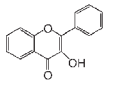
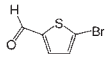
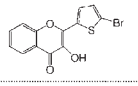
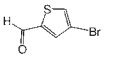
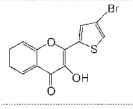
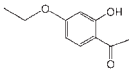
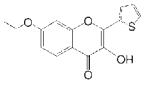
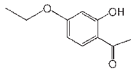
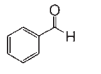
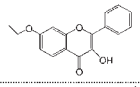
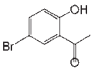
Table 1. Synthesized 3HF[a]

entry	ketones (**K**)	aldehydes (**A**)	3HF	yield (%)	reaction time
1				65	5 h
2				44	5 h
3				40	5 h
4				35	5 h
5				76	2 h
6				65	2 h
7				56	3 h
8				79	3 h
9				75	2 h
10				55	3 h
11				52	3 h
12				55	3 h
13				50	4 h
14				52	3 h
15				70	3 h
16				64	3 h
17				65	2 h

[a] Experimental conditions: (i) NaOH (solid), MeOH, reflux; (ii) NaOH (0.5 N), H_2O_2. While **P1**–**P4** were extracted with EtOAc, **P4**–**P17** were filtered after the crude product was poured into ice-water (see the Supporting Information for the experimental details).

fluorescence spectra, originated from normal (N*) and phototautomer forms (T*) of an excited state intramolecular proton transfer (ESIPT) reaction.[6] The ratio of the intensities of these two bands is strongly sensitive to the environment of the molecule, including polarity[7] and hydrogen bonding perturbations in proteins,[8] micelles,[9] and polymers.[10] Recently, the ESIPT property of 3HF enabled the synthesis of an analogue of 3HF, **P10** (Table 1, entry 10), incorporating thiophene in place of phenyl ring B, as a material for bulk heterojunction solar cells.[11]

In our search for the synthesis of new 3HFs, particularly having a hydroxyl group on ring B, a more efficient synthetic method was developed with modifications of the current synthetic methods, which led to the syntheses of various 3HF derivatives, including 3HFs having a 4-hydroxyl group on ring B. The syntheses were achieved with higher yields and shorter reaction times and were easy to isolate with no intermediate and side product such as chalcone and aurone, respectively (Table 1). One can realize that, in spite of the importance of 3HFs, there are limited synthetic methods available in the literature, the oldest of which is Auwers synthesis.[12] As it consists of a series of reactions, currently, the more modern Algar–Flynn–Oyamada (AFO) reaction is widely applied.[11,13] However, it is not a very efficient one as well. It involves a couple of steps such as the preparation of chalcone and its oxidative cyclization reaction, which results in two products, 3HF and aurone. Moreover, the reaction requires a long reaction time (such as days or, if lucky, overnight) to complete, tedious workup, and isolation processes of the products. The reaction yields are no more than 40%, in general ~15–35%.[5h,6b,c,7,14]

Concerning the synthesis of 3HF **P1**, having a hydroxyl group on ring B, the synthesis available in the literature involves four steps, starting with the reaction of 2-hydroxyacetophenone **K1** with 4-methoxybenzaldehyde **2**, and the whole synthesis requires 113 h to complete (Figure 2).[15] To obtain **P1** in one step, we reacted 2-hydroxyacetophenone **K1** with 4-formylphenylboronic acid **A1** (Table 1, entry 1). Unfortunately all our attempts applying conventional reaction methods did not give any satisfactory result. On the other hand, when the reaction was performed in refluxing methanol in the presence of solid sodium hydroxide for 5 h, followed by in situ oxidative cyclization with hydrogen peroxide at room temperature, **P1** was obtained in one step with a relatively high yield, 65%, by simply extracting the crude product, which did not require any further purification (see Supporting Information for experimental details). In order to understand if the new modified reaction condition will be successful with hydroxyphenylaldehydes to obtain the 3HFs **P1**–**P4**, attempts were performed with the reactions of 4-hydroxybenzaldehde and 2-hydroxy-5-nitrobenzaldehyde **A4** with ketones **K1**–**K4**. Although all attempts for the syntheses of flavones **P1**–**P3** failed, **P4** was successfully obtained in moderate yield, 35% (Table 1, entry 4). This could be due to a greater sensitivity of the *para* hydroxyl substituted phenyls to the environment, compared with the *ortho* hydroxy substituted one.

Two more 3HFs having a 4′-hydroxyphenyl moiety were synthesized satisfactorily in moderate yields, 44 and 40%, applying a new reaction condition to 4- formylphenylboronic acid (Table 1, entries 2 and 3). Then, since such a successful new reaction procedure is now available, we decided to apply it to the syntheses of a series of 3HFs **P5**–**P17**, reacting the corresponding ketones **K5**–**K17** with aldehydes **A5**–**A17**, respectively, which included the 3HF analogue **P10** for bulk heterojunction solar cells, mentioned above.[11] (Table 1, entries 5–17, entry 10, respectively). New reactions gave the 3HFs in shorter reaction times (2, 3 h) and with better yields, even reaching 79%. **P10** was obtained in 55% yield in 3 h, which was reported to be synthesized in two steps, overnight, with an overall yield of 26%.

Fluorescence spectra of the 3HFs displayed two bands, N* and T*, between 309–505 and 480–608 nm, respectively, which are a typical indication of ESIPT reactions of 3HFs (Table 2, see Supporting Information).

Environmental sensitivity (solvatochromic effect) of the 3HFs was demonstrated with the flavone **P1**, which, upon

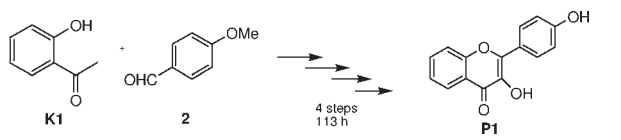


Figure 2. Literature synthesis of 3HF, having hydroxyl on ring B.[14]

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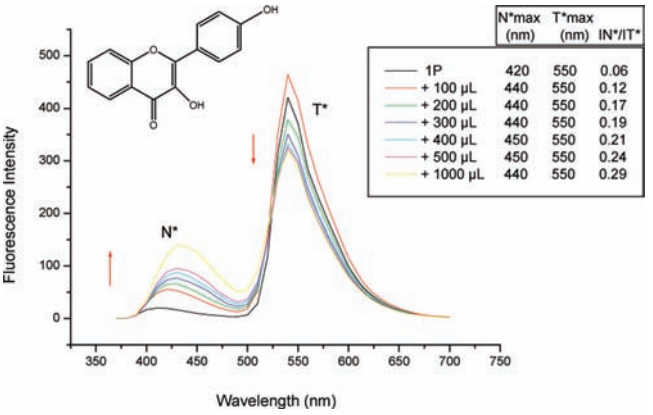

Figure 3. Fluorescence spectra of 3HF **P1** (0.165 mM in THF), titrated with H_2O.

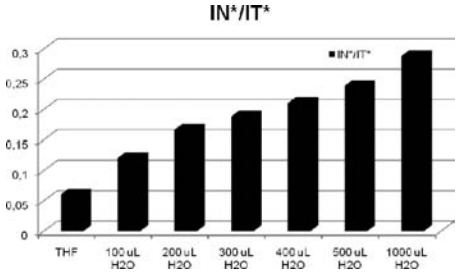

Figure 4. Ratiometric change of N*/T* fluorescence band intensities of **P1** upon addition of water.

addition of water, exhibited a ratiometric increase and decrease of N* and T* bands, respectively (Figure 3). A linear ratiometric change of the two bands was depicted in Figure 4.

In conclusion, a rapid and more efficient method than the methods available in the literature has been developed. It is applicable to the syntheses of various 3HFs, including

Table 2. Spectroscopic Data of 3HF Derivatives[a]

3HF	$\lambda^{abs}{}_{max}$	$\lambda^{N*}{}_{max}$	$\lambda^{T*}{}_{max}$	solvent	I_{N*}/I_{T*}	QY
P1	351	419	536	acetone	0.076	0.10
P2	356	420	530	CH_2Cl_2	0.025	0.10
P3	346	401	533	CH_2Cl_2	0.009	0.13
P4	414	353	496	DMSO	6.03	0.09
P5	346	420	530	CH_2Cl_2	0.04	0.22
P6	317	418	532	CH_2Cl_2	0.003	0.07
P7	349	418	525	CH_2Cl_2	0.002	0.29
P8	400	488	567	CH_2Cl_2	0.446	0.09
P9	343	392	522	CH_2Cl_2	0.007	0.18
P10	364	423	548	CH_2Cl_2	0.12	0.21
P11	460	393	545	acetone	0.017	0.26
P12	448	398	551	acetone	0.011	0.17
P13	321	394	532	CH_2Cl_2	0.004	0.06
P14	329	502	580	EtOAc	0.68	0.03
P15	355	399	547	acetone	0.014	0.20
P16	457	406	551	acetone	0.024	0.17
P17	349	410	543	acetone	0.04	0.11

[a] $\lambda^{abs}{}_{max}$, absorption maxima; $\lambda^{N*}{}_{max}$ and $\lambda^{T*}{}_{max}$, fluorescence maxima of N* and T* bands. Fluorescence quantum yields (QY) were measured using anthracene in ethanol as a reference.

3HFs having a hydroxyl group on the phenyl ring B. The reaction does not lead to any side products, and 3HFs can be isolated from the reaction mixture by simple filtration, which are pure enough for further use. As the current methods produce lower yields with various side products, which make their isolation difficult, the method presented herein will be useful for the syntheses of wide variety of 3-hydroxyflavones.

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Supporting Information Available. Detailed experimental procedures and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.