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Friedel-Crafts reactions in water of carbonyl compounds with heteroaromatic compounds

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The development of Friedel-Crafts reaction in H_2O of carbonyl compounds is presented; a series of different heteroaromatic compounds react with ethyl glyoxylate to give the Friedel-Crafts addition adducts in good yields in various H_2O solutions.

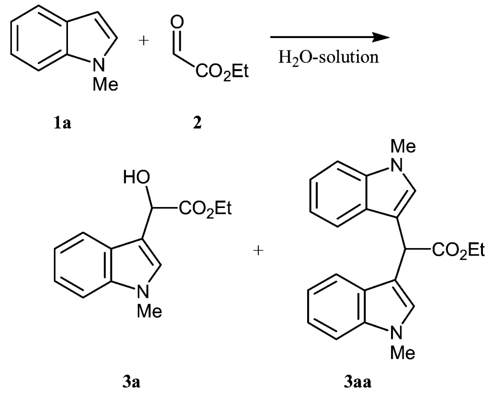
One of the fundamental challenges and ultimate goals for reactions of organic molecules is to perform the reaction in water,[1] because the application of water would reduce the use of harmful organic solvents and lead to the development of environmentally friendly processes.

A further challenge is to perform catalytic organic reactions in water, which normally require strict reaction conditions in organic solvents in order for the catalyst to be usable. In recent years focus has been on Lewis-acid catalyzed organic reactions in water and several important reactions are beginning to be developed.[2]

The Friedel-Crafts reaction is one of the most important Lewis-acid catalyzed reactions for the formation of C–C bonds to aromatic compounds.[3] These reactions normally require one equivalent of a strong Lewis acid, such as $AlCl_3$, and strict reaction conditions in order to proceed.[3] A major step towards more environmentally friendly conditions for this important class of reactions would be to perform the reactions in water and without the use of the traditional Lewis-acid catalysis.[4]

This communication shows that Friedel-Crafts reactions of activated carbonyl compounds with heteroaromatic compounds can successfully take place in H_2O without the normally used Lewis/Brønsted acid catalysts.[5,6]

The reaction of *N*-methylindole **1a** with ethyl glyoxylate **2**† [eq. (1)] was used for the screening process. Table 1 shows some results from the screening and optimisation process.



(1)

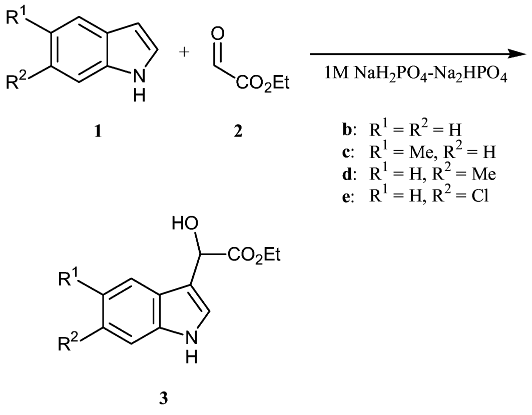
In a 1M Na_2CO_3 solution (pH 11.3) *N*-methylindole **1a** reacts with ethyl glyoxylate **2** to give the Friedel-Crafts addition adduct **3a** in only 17% yield (Table 1, entry 1). However, reducing the basicity of the Na_2CO_3–H_2O solution (pH 8.7–7.5) leads to a solvent composition where a smooth Friedel-Crafts reaction takes place and **3a** was isolated in up to 90% yield (entries 2–7). If the H_2O solution is slightly acidic (pH 7.5–6.4) applying a NaH_2PO_4–Na_2HPO_4 buffer system, the amount of double addition adduct **3aa** formed increases (entries 8–10), and at pH 6, 54% of **3aa** is formed in excess (entry 10). Performing the Friedel-Crafts reaction in a 1M $NaHSO_4$ solution (pH = 5.5), a 1M NaCl solution (pH = 7) and in distilled H_2O (pH = 7) only the double addition adduct **3aa** is formed (entries 10–13).

Table 1 Reaction of *N*-methylindole **1a** with ethyl glyoxylate **2** in various H_2O solutions

Entry	Solution	pH	Yield **3a**[a] (%)	Yield **3aa**[a] (%)
1	1M Na_2CO_3	11.3	17	0
2	Sat. $NaHCO_3$	8.7	87	0
3[b]	Sat. $NaHCO_3$	8.7	95	0
4	1M $NaHCO_3$	8.0	87	0
5[b]	1M $NaHCO_3$	8.0	90	0
6	1M $KHCO_3$	8.0	74	0
7	NaH_2PO_4–Na_2HPO_4	7.5	87	0
8	NaH_2PO_4–Na_2HPO_4	7.1	82	2
9	NaH_2PO_4–Na_2HPO_4	6.4	63	16
10	NaH_2PO_4–Na_2HPO_4	6.0	34	54
11	1M $NaHSO_4$	5.5	0	74
12	1M NaCl	7.0	0	68
13	H_2O	7.0	0	62

[a] Isolated yield. [b] Double amount of ethyl glyoxylate **2** relative to *N*-methylindole.

The results in Table 1 show that the $NaHCO_3$–H_2O solution has unique properties for the Friedel-Crafts reaction and it should be noted that no Friedel-Crafts product is formed if *e.g.* *N*-methylindole **1a** and ethyl glyoxylate **2** are mixed in an organic solvent such as CH_2Cl_2 in the absence of a catalyst. It is interesting also to compare the reaction conditions for the present reaction which takes place in water, with *e.g.* the reaction of a closely related α-carbonyl ester, ethyl pyruvate, with aromatic compounds, which proceeds only in dry organic solvents using $AlCl_3$ or $TiCl_4$ (one equivalent).[7] Furthermore, it should be emphasized that Lewis-acid catalyzed reactions of glyoxylates normally require that the glyoxylate is freshly distilled before use. For the present reaction ethyl glyoxylate can be used directly after preparation from maleate,†from which it exists to a high extent as a polymer, without taking any precautions.



(2)

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The results for Friedel-Crafts reaction for a series of different indoles **1b–e** with ethyl glyoxylate **2** [eq (2)] and using a buffer solution (1M NaH_2PO_4–Na_2HPO_4) are presented in Table 2.

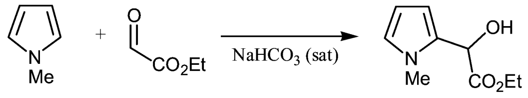
Table 2 Reaction of different indoles **1b–e** with ethyl glyoxylate **2** in a 1M NaH_2PO_4–Na_2HPO_4

Entry	Indole	Reaction time (h)	pH	Yield[a] (%)
1	**1b**	4	7.1	**3b** – 67
2	**1c**	4	6.8	**3c** – 84
3	**1d**	4	6.8	**3d** – 70
4	**1e**	30	6.8	**3e** – 62

[a] Isolated yield.

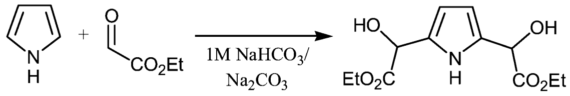
The reaction of the indoles having both electron-donating and electron-withdrawing substituents (**1b–e**) proceeds well with ethyl glyoxylate **2** in the 1M NaH_2PO_4–Na_2HPO_4 buffered solution and the Friedel-Crafts adducts **3b–e** are all isolated in good yields (Table 2, entries 1–4).

The Friedel-Crafts reaction also proceeds well for pyrroles in water; *e.g. N*-methylpyrrole **4a** reacts with ethyl glyoxylate **2** in a saturated $NaHCO_3$ solution to give the **5a** in 87% yield [eq (3)].[8] The Friedel-Crafts reaction of **2** with pyrrole **4b** reacts in a 1M $NaHCO_3$–Na_2CO_3 solution to give to double addition of ethyl glyoxylate to both the 2- and 5-positions of **4b** and adduct **5b** is obtained in 63% yield by using a large excess of **2** [eq (4)].



(3)

4a **2** **5a**



(4)

4b **2** **5b**

The results show that the $NaHCO_3$–H_2O solution has unique properties for the Friedel-Crafts reaction. However, at the present stage of investigations we do not yet have sufficient mechanistic details to account for the role of the solvent composition in the selectivity of the reaction.

In summary, we have demonstrated the first Friedel-Crafts reactions of carbonyl compounds with heteroaromatic compounds in water without the use of the traditional Lewis acid catalysis. The reactions proceed well for various indoles and the Friedel-Crafts adducts are obtained in high yields. For pyrroles, both addition to the 2-, as well as the 2- and 5-positions are obtained depending of the amount of ethyl glyoxylate used. Further work is in progress to develop catalytic enantioselective Friedel-Crafts reactions in water.

We are indebted to The Danish National Research Foundation for financial support.

Notes and references

† Procedure for preparing ethyl glyoxylate **2**: A 500 ml round bottle flask containing diethyl maleate (40 g) dissolved in 250 ml dry CH_2Cl_2 was bubbled with O_3 at −78 °C. When the colour of the solution changed to blue, the reaction was quenched by 1.05 eq. Me_2S at −78 °C and then slowly warmed up to room temperature. After concentration in vacuum at room temperature, the crude ethyl glyoxylate was kept at −24 °C.

General reaction conditions: Representative experimental procedure: To a 10 ml tube was added 1M NaH_2PO_4–Na_2HPO_4 solution (2 ml). Subsequently, 5-methylindole **1c** (65.6 mg, 0.50 mmol) and non-distilled ethyl glyoxylate **2** (0.25 ml) were added and reacted for 4 h. The solution was adjusted to pH = 10 by sat. $NaHCO_3$, then extracted by CH_2Cl_2, dried by $MgSO_4$. The product **3c** was obtained by flash chromatography (10% Et_2O in CH_2Cl_2) in 84% yield. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.19 (s, 1H, NH), 7.50 (s, 1H; Ar), 7.21 (d, J = 8.4 Hz, 1H; Ar), 7.10 (d, J = 2.8 Hz, 1H; Ar), 7.03 (dd, J = 8.4, 1.2 Hz, 1H; Ar), 5.43 (d, J = 6.0 Hz, 1H; CH), 4.30 (dq, J = 10.8, 6.8 Hz, 1H; CH_2CH_3), 4.16 (dq, J = 10.8, 6.8 Hz, 1H; CH_2CH_3), 3.36 (d, J = 6.0 Hz, 1H; OH), 2.45 (s, 3H; CH_3), 1.23 (t, J = 6.8 Hz, 3H; CH_2CH_3); ^{13}C NMR (100 MHz) δ 174.4, 135.0, 129.7, 125.8, 124.4, 123.7, 119.2, 113.4, 111.3, 67.6, 62.3, 21.8, 14.3; HRMS $C_{13}H_{15}NO_3$ $[M + Na]^+$ calculated 256.0950 found 256.0952.

1 See *e.g.*: *Organic Synthesis in Water*, ed. P. A: Grieco, Blackie Academic and Professional, London, 1998; C.-J. Li and T. H. Chan, *Organic Reactions in Aqueous Media*, John Wiley and Sons, New York, 1997; C.-J. Li, *Chem. Rev.*, 1993, **93**, 2023; R. Breslow, *Acc. Chem. Res.*, 1991, **24**, 159.

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7 A. Citterio, M. Gandolfi, O. Piccolo, L. Filippini, L. Tinucci and E. Valoti, *Synthesis*, 1984, 760.

8 When a large excess of ethyl glyoxylate was used, the product of double addition to both the 2- and 5-position of **4a** was found.