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Mannich reactions catalyzed by perchloric acid in Triton X10 aqueous micelles

Guo-ping Lu, Chun Cai *

School of Chemical Engineering, Nanjing University of Science and Technology, 200 Xiaoling Wei, Nanjing 210094, China

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ABSTRACT

Perchloric acid can efficiently catalyze the one-pot, three-component Mannich reactions of ketones with aromatic aldehydes and aromatic amines in Triton X10 aqueous micelles at room temperature. This protocol has several advantages such as excellent yields, mild conditions, clear reaction profile and simple work-up procedure.

1. Introduction

Recently, water as a sole medium for organic reactions has received considerable attention in synthetic organic chemistry for several reasons. First, water as a cheap, abundant, non-toxic, non-flammable solvent is more suitable for industrial production than toxic and expensive organic solvents [1–4]. Second, in aqueous reactions, it is unnecessary to dry solvents, substrates and reagents before use. Third, water with its chemical and physical properties imposes unique selectivity and reactivity in reactions conducted in aqueous media which cannot be gained using organic solvents [5–9].

Nevertheless, in many cases, the poor solubility of reactants and the deleterious effect on many organic transformations are the main obstacles to use water as reaction medium. An intriguing means of achieving aqueous solubility is by using surfactants in water to form micelles which appear to be homogeneous since these aggregates are of colloidal size, however, in reality the absorbed reactants are in a microheterogeneous system [10]. It can cause an acceleration of many organic reactions relative to the equivalent reaction in aqueous medium which refers to as "micellar catalysis" [11–14].

Mannich reaction as one of the most important carbon–carbon bond forming reactions provides β-amino carbonyl compounds, which are important synthetic intermediates for various pharmaceuticals and natural products [15–21]. To replace expensive, toxic, flammable organic solvents with water, Mannich and related reactions being carried out in water have attracted much attention [22–29]. However, most of reactions required long reaction time in the presence of different catalysts (Table 1). To develop new protocols to pronounced catalyze Mannich reactions in water, we have found perchloric acid to be an efficient catalyst in Triton X10 (TX10) aqueous micelles at room temperature for the synthesis of β-amino carbonyl compounds (Scheme 1).

2. Experimental

2.1. Materials and characterization

Melting points were determined uncorrected. ^{1}H NMR spectra were recorded on Bruker DRX500 (500 MHz) or Bruker DRX500 (300 MHz) and ^{13}C NMR spectra on Bruker DRX500 (125 MHz) spectrometer. Triton X10 (Polyoxyethylene(10) octylphenyl ether, TX10) was purchased from the petrochemical plant of Jiangsu Haian. All other chemicals (AR grade) were commercially available and used without further purification. All products are known compounds and identified by physical data (m.p.) or ^{1}H NMR with those reported in the literature.

2.2. Mannich reactions catalyzed by perchloric acid in TX10 aqueous micelles

To a solution of 5 wt.% TX10 aqueous micelles (4.0 ml) were added amine (2.5 mmol), aldehyde (2.5 mmol), and ketone (2.5 mmol) successively at room temperature. Perchloric acid (0.25 mmol, as a 70 wt.% aqueous solution) was added, and the mixture was stirred at the same temperature for the period of time listed in Table 3. After the reaction completed, water (10.0 ml) was

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* Corresponding author. Tel.: +86 25 84315514; fax: +86 25 84315030.
E-mail address: c.cai@mail.njust.edu.cn (C. Cai).

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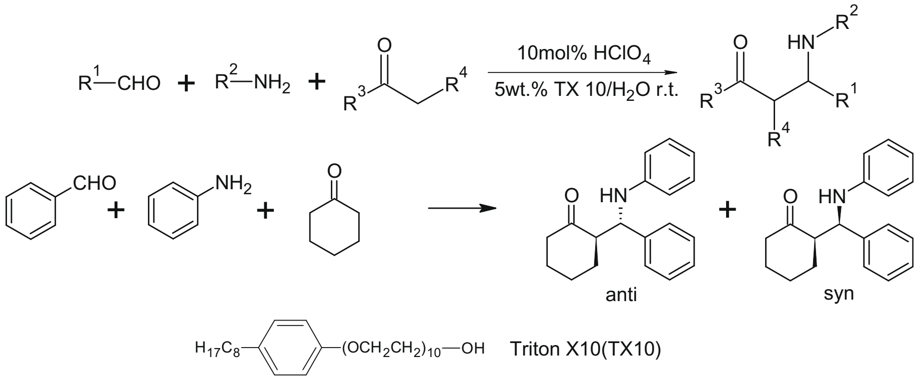
Table 1
Different catalytic systems for the Manncih reaction of benzaldehyde, aniline, and acetophenone.

Entry	Catalyst	Reaction medium	Time (h)	Yield (%)	Reference
1	HCl	SDS/H_2O	24	98	[20]
2	$NaBArF_4$	H_2O	48	81	[22]
3	$H_3PW_{12}O_{40}$	H_2O	18	76	[25]
4	FQAS/TsOH	H_2O	12	70	[26]
5	DBSA	H_2O	24	63	[27]
6	$C_6H_{11}N(C_6H_4)_2Bi(OSO_2C_8F_{17})$	H_2O	36	30	[28]
7	[cmmim][BF_4]	[bmim]BF_4/H_2O	12	90	[29]
8	$HClO_4$	TX10/H_2O	6	92	–



Scheme 1. Mannich reactions in TX10 aqueous micelles.

added to the mixture, and the solid precipitated was separated with a simple filtration, washed with water and dried to afford the desired product.

2.2.1. 2-[1′-(N-phenylamino)-1′-(p-dimethylaminophenyl)] methylcyclohexanone (Table 3, entry 17)

A light yellow solid; m.p. 160–162 °C; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.56–1.72 (m, 4H), 1.84–1.94 (m, 4H), 2.45–2.53 (m, 1H), 2.94 (s, 6H), 3.04 (s, 1H), 4.57 (d, 0.65H, anti, $J = 7.5$ Hz), 4.72 (d, 0.35H, syn, $J = 4$ Hz), 6.57–6.60 (m, 2H), 6.63–6.66 (m, 1H), 6.69–6.78 (m, 2H), 7.06–7.11 (m, 2H), 7.17–7.28 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 23.28, 27.87, 30.87, 40.62, 41.46, 42.41, 56.71, 57.71, 112.55, 112.62, 113.81, 114.08, 117.41, 128.00, 128.29, 128.99, 129.26, 129.27, 147.33, 149.48, 213.26.

3. Results and discussion

In order to optimize the reaction conditions, the reaction of benzaldehyde, aniline, and acetophenone was selected as a model reaction. When feasible, the use of Brønsted acids to catalyze organic reactions in water is one of the most convenient and environmentally benign methods, and TX10 as a cheap, non-toxic surfactant is widely applied in industry for emulsifier, detergent and so on, so we first studied the reaction in TX10 aqueous micelles with different Brønsted acids as catalysts (Table 2, entries 1–3, 5). The yield was highest, when perchloric acid was used as catalyst. After screening different reaction medium (Table 2, entries 4–9), 5 wt.% TX10 aqueous micelles proved to be the best choice. In order to verify the merit of the TX10 aqueous micelles, the reaction was run in the absence of TX10 under similar conditions, as a

Table 2
Optimization of the reaction conditions.[a]

Entry	Catalyst (10 mol%)	Reaction medium (4 ml)	Yield (%)[b]
1	HCl	5 wt.% TX10/H_2O	Trace
2	TsOH[c]	5 wt.% TX10/H_2O	48
3	CF_3COOH	5 wt.% TX10/H_2O	16
4	$HClO_4$	2 wt.% TX10/H_2O	73
5	$HClO_4$	5 wt.% TX10/H_2O	92
6	$HClO_4$	10 wt.% TX10/H_2O	89
7	$HClO_4$	CH_3COCH_3	Trace
8	$HClO_4$	CH_2Cl_2	62
9	$HClO_4$	C_2H_5OH	81
10	$HClO_4$	H_2O	19
11	None	5 wt.% TX10/H_2O	Trace

[a] Reaction condition: benzaldehyde 2.5 mmol, aniline 2.5 mmol, acetophenone 2.5 mmol, room temperature, 6 h.

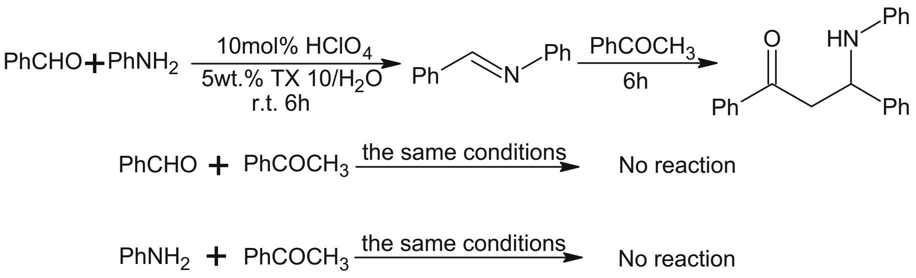
[b] Isolated yields.

[c] TsOH is 4-toluenesulfonic acid.

Table 3
Perchloric acid-catalyzed direct Mannich reactions of various aromatic aldehydes and aromatic amines with different ketones.[a]

Entry	Time (h)	Ketone		Aldehyde	Amine	Yield (%)[b]	M.p. (°C)/(lit.)
		R^3	R^4	R^1	R^2		
1	6	Ph	H	Ph	Ph	92	167–169(168–170)[30]
2	4	Ph	H	4-$(CH_3)_2NC_6H_4$	Ph	93	200–202(202–203)[21]
3	10	Ph	H	4-$CH_3OC_6H_4$	Ph	91	148–150(147–149)[30]
4	10	Ph	H	4-$O_2NC_6H_4$	Ph	Imine[c]	–
5	12	Ph	H	4-ClC_6H_4	Ph	91	130–132(131–132)[30]
6	12	Ph	H	4-BrC_6H_4	Ph	89	128–130(130–131)[30]
7	6	Ph	H	Ph	4-ClC_6H_4	97	164–166(166–167)[18]
8	12	Ph	H	Ph	3-$O_2NC_6H_4$	98	142–144(140–142)[18]
9	18	Ph	H	Ph	4-$CH_3C_6H_4$	83	168–170(168–170)[18]
10	18	Ph	H	Ph	4-$O_2NC_6H_4$	80	177–179(177–178)[30]
11	6	4-$O_2NC_6H_4$	H	Ph	Ph	95	144–146(144–146)[18]
12	6	4-ClC_6H_4	H	Ph	Ph	94	119–121(119–120)[18]
13	8	4-$CH_3C_6H_4$	H	Ph	Ph	88	136–138(138–139)[18]
14	24	Ph	H	2-ClC_6H_4	Ph	Trace	–
15	24	Ph	H	Ph	2-$CH_3C_6H_4$	Trace	–
16	1	Cyclohexanone		Ph	Ph	97(99:1)[d]	137–139(135–137)[26]
17	1	Cyclohexanone		4-$(CH_3)_2NC_6H_4$	Ph	84(65:35)	160–162
18	2	Cyclohexanone		2-$O_2NC_6H_4$	Ph	90(61:39)	154–156
19	1	Cyclohexanone		Ph	4-ClC_6H_4	98(76:24)	135–137(137–138)[18]
20	10	CH_3CH_2	CH_3	Ph	Ph	89(100:0)	128–130

[a] Reaction condition: aldehyde 2.5 mmol, amine 2.5 mmol, ketone 2.5 mmol, $HClO_4$ 0.25 mmol, 5 wt.% TX10/H_2O 4 ml, room temperature.
[b] Isolated yields.
[c] The final product was imine formed from the reaction of 4-nitrobenzaldehyde and aniline.
[d] Anti/syn ratio, determined by ^1H NMR.



Scheme 2. Chemoselectivity of acetophenone to aldimine.

result, the reaction was sluggish and only 19% of desired product was gained (Table 2, entry 10). On the other hand, a very low yield of product was obtained in the 5 wt.% TX10 aqueous micelles in the absence of perchloric acid (Table 2, entry 11).

With the optimized conditions in hand, the reactions of various aromatic ketones, aromatic aldehydes and aromatic amines were examined to ascertain the generality and scope of the protocol (Table 3, entries 1–15). There are several noteworthy features in these reactions as follow. (1) It was found that both electron-rich and electron-deficient benzaldehydes resulted in good yields, but only imine could be obtained as the final product for the benzaldehyde with strong electron-withdrawing group such as nitro group (Table 3, entry 4). (2) The reaction was not affected obviously by the characteristics of the substituent group on aniline or acetophenone. (3) Generally, the ortho-substituted aromatic amines and aromatic aldehydes gave trace of the desired products because of large steric hindrance effect (Table 3, entries 14 and 15).

The remarkable results obtained with this protocol promoted us to use cyclohexanone under these conditions (Table 3, entries 16–19). The results indicated that cyclohexanone was more active than acetophenone, because its enol formation was much faster than acetophenone. Instead of cyclohexanone, 3-pentanone also gave a good yield of product (Table 3, entry 20). The results of the anti/syn ratios (Table 3, entries 16–20) indicated it was feasible to get high stereoselectivity product by the protocol in some cases.

To explore the mechanism of Mannich reactions in aqueous micelles, we performed experiments as shown in Scheme 2. Only the reaction of benzaldehyde with aniline could take place to obtain corresponding imine, which then could react with acetophenone to form the β-amino carbonyl compound under the same conditions. It could be concluded that when the reaction of aldehyde, amine and ketone occurred, the aldehyde could coordinate with amine to form an iminium ion in the presence of perchloric acid at first, and then it was followed by insertion of the C=N bond into ketone to produce the β-amino carbonyl compound. If the electrophilicity of the iminium ion is not enough to react with the ketone, only the corresponding imine is obtained as final product (such as Table 3, entry 4). The catalytic effect of TX10 micelles in Mannich reactions could be explained as shown in Fig. 1. In TX10 aqueous micelles, according to substrates polarity, they were buried in hydrophobic cores. On one hand, due to the huge interfacial area in micelles, the catalyst could contact with substrates sufficiently. On the other hand, micelle droplets formed by TX10 with substrates were hydrophobic enough to exclude water molecules [7], making it easy to form the iminium ion. Thus, the reaction occurred more easily in a micelle special with respect to its functioning as a micro- or nanoreactor [10].

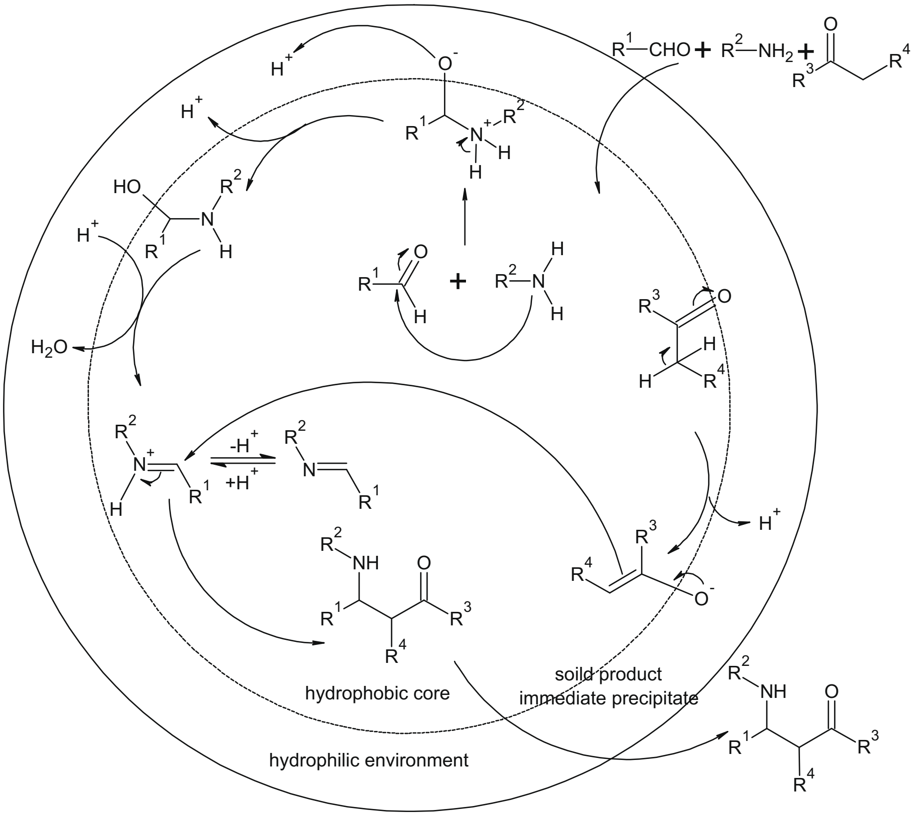


Fig. 1. Tentative mechanism of Mannich reactions in aqueous micelles.

4. Conclusions

In conclusion, Mannich reactions catalyzed by perchloric acid can be performed in TX10 aqueous micelles effectively. The procedure provides several advantages, such as shorter reaction time, mild conditions, high yields, good stereoselectivities and clear reaction profile. In addition, all products are solid and insoluble in water, so they can be obtained directly by filtration.

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