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Mannich-type reactions in a colloidal solution formed by sodium tetrakis(3,5-trifluoromethylphenyl)borate as a catalyst in water

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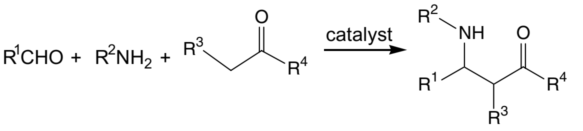
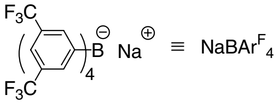
Abstract—Sodium tetrakis(3,5-trifluoromethylphenyl)borate [$NaBAr_4^F$] efficiently catalyzed the one-pot, three-component Mannich reaction of ketones with aromatic aldehydes and different anilines in water at an ambient temperature and afforded the corresponding β-amino carbonyl compounds in good to excellent yields.

The Mannich reaction is one of the most important carbon–carbon bond forming reactions in organic synthesis, Eq. 1.[1] This reaction provides the formation of β-amino carbonyl compounds, which are important intermediates for the construction of various nitrogen-containing natural products and pharmaceuticals.[2] However, the drastic reaction conditions for the classical intermolecular Mannich reaction limit its synthetic usefulness. Therefore, numerous modifications of this reaction have been developed to overcome the drawbacks.[1,3] Many metal complexes have been used as Lewis acid catalysts to promote the reaction under anhydrous conditions,[1–3] and few water-compatible Lewis acids were reported.[4]



(1)

In recent years, organic reactions in an aqueous medium have received enormous attention, because the use of water has several advantages as it is the easiest obtainable solvent, is an environmentally friendly substance, and can be easily separated from organic products.[5–7] In this context, researches focusing on the development of new catalysts to promote organic reactions in water have become highly desirable. In an early report Kobayashi and Manabe, they found that dodecylbenzenesulfonic acid could catalyze the Mannich reaction at an ambient temperature in water to give various β-amino ketones in good yields.[6] In these surfactant-aided systems, organic substrates form emulsion droplets that function as reaction media in water. However, the presence of a Brønsted acid is still required to carry out the reaction in most of the instances. Here, we offer an efficient method for the preparation of Mannich type products in water by using sodium tetrakis(3,5-trifluoromethyl-phenyl)borate ([$NaBAr_4^F$]) as a catalyst under mild and nearly neutral conditions.



Initially, the two-component Mannich reaction of *N*-benzylideneaniline (1.0 mmol) and various nucleophiles (2 mmol) was examined (Table 1). As a preliminary study, we found that [$NaBAr_4^F$] did not catalyze the reaction of acetophenone with benzylideneaniline in most of the organic solvents such as THF, dichloromethane or DMF. It was revealed that the present Mannich-type reaction proceeded only in aqueous media. Running the reaction of benzylideneaniline with ketone in water at an ambient temperature gave the desired product in an excellent yield (Table 1, entry 4). Encouraged by the results, we examined various ketones and silyl enolates to screen the scope of this new protocol. The silyl

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Table 1. Results of Mannich reaction catalyzed by $[\mathrm{NaBAr}^{\mathrm{F}}_4]$[a]

Entry	Ketone or silyl enol ether	Solvent	Time	Yield (%)
1	Acetophenone	CH_2Cl_2	96 h	0
2	Acetophenone	THF	96 h	0
3	Acetophenone	DMF	96 h	Trace
4	Acetophenone	Water	96 h	96
5	$C_6H_5C(OSiMe_3){=}CH_2$	Water	30 min	91
			1 h	100
6	$C_6H_5C(OSiMe_3){=}CHCH_3$	Water	30 min	77
			1 h	100
7	$C_6H_5C(O)CH_2CH_3$	Water	144 h	32
8	Cyclohexone	Water	3 h	100

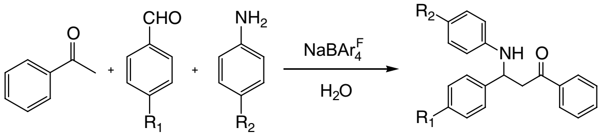
[a] Reaction conditions: $[\mathrm{NaBAr}^{\mathrm{F}}_4]$ (0.005 mmol), ketone or silyl enol ether (2 mmol), *N*-benzylideneaniline (1 mmol) at 30 °C.

enolate as the nucleophile in the reaction appeared to be more reactive than the corresponding ketone compounds as evidenced by the shorter reaction time and better yields (Table 1, entries 5 and 6).

With the success of the above coupling reaction, we examined the feasibility of the three-component Mannich reaction. The reaction of benzaldehyde, aniline, and acetophenone in the presence of $[\mathrm{NaBAr}^{\mathrm{F}}_4]$ as the catalyst in water provided the desired compound in an 81% isolated yield (Table 2, entry 1). Again, this efficient catalyst was not observed in the reactions carried out in the organic solvents. Several of the substituted anilines underwent the reaction smoothly except for *p*-nitroaniline (Table 2, entry 9). By using ^{1}H NMR to monitor the reaction, we realized that the imine intermediate, 4-nitrobenzylidenephenylamine, was not formed during the reaction.

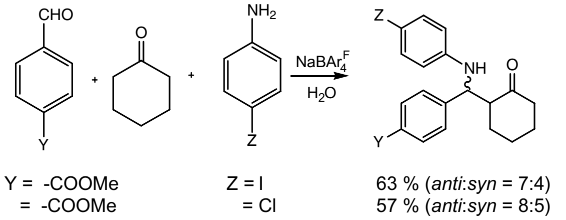
The reactions proceeded not only for acetophenone but also for other dialkyl ketones in good yields. As illustrated in Scheme 1, $[\mathrm{NaBAr}^{\mathrm{F}}_4]$ did catalyze the Mannich reaction of cyclohexone, substituted benzaldehydes, and anilines to yield the desired β-amino ketone products. The stereoselectivity was determined by ^{1}H NMR spectroscopy and by comparison with known compounds.

Table 2. Results of the three-component Mannich reaction[a]



Entry	R_1	R_2	Time (h)	Yield (%)
1	H	H	48	81
2	F	H	48	51
3	Cl	H	48	74
4	Br	H	48	85
5	*i*-Propyl	H	48	53
6	CH_3O	H	48	21
7	H	I	24	100
8	H	Me	24	51
9	H	NO_2	48	—

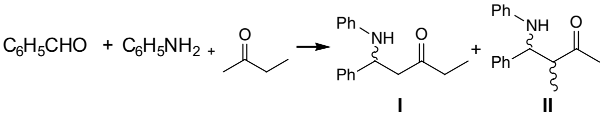
[a] Reaction conditions: $[\mathrm{NaBAr}^{\mathrm{F}}_4]$ (0.005 mmol), acetophenone (2 mmol), aniline (1 mmol), aldehyde (1 mmol) in H_2O (2 mL) at 30 °C.



Scheme 1.

The selectivity for *anti*-isomers is slightly favored. In addition, the reaction of cyclohexanone and *p*-chloroaniline with 1-naphthalenecarbaldehyde yielded the coupling product, 2-[(4-chlorophenylamino)naphthalen-1-ylmethyl]-cyclohexanone, in 65% (*anti*:*syn* = 1:1).

For unsymmetric ketone, the regioselectivity of the less hindered site is observed. Thus, the reaction of 2-butanone, benzaldehyde, and aniline in the presence of $[\mathrm{NaBAr}^{\mathrm{F}}_4]$ in water provided Mannich products **I** and **II**, Eq. 2. The ratio of **I**:**II** is about 85:15, indicating that the reaction takes place at the less substituted carbon center.



(2)

It should be noted that the addition of organic substrates to this sodium salt in water readily formed a milky suspension, indicating that borate anions acted as surfactants.[8] In an early work, we found this salt did not completely dissociate into free ions in dichloromethane, with the formation of aggregation instead.[9] From the dynamic light scattering measurement, the average size of aggregated particles of $[\mathrm{NaBAr}^{\mathrm{F}}_4]$ and organic substrates is in the range of ~1 μm. Thus the addition of organic substrates readily forms a colloidal dispersion, which is similar to that of a mixture of dodecylbenzenesulfonic acid (DBSA) and organic reagents in water reported by Kobayashi and Manabe.[6] Apparently, the formation of colloid particles plays an essential role in the acceleration of the coupling reaction. In our early study, the crystal structure of $[\mathrm{NaBAr}^{\mathrm{F}}_4]$ reveals that the fluorine atoms of trifluoromethyl groups do coordinate toward the metal center.[9] We believe that such coordination might partially persist in an aqueous environment, which thus increases the Lewis acidity of metal ions.

In conclusion, this procedure offers several advantages for the Mannich reaction such as low loading of catalyst, mild conditions, high yields, clean reactions, which make it a useful and attractive methodology for organic synthesis. Quite a number of products are solid and insoluble in water, which can be obtained by filtration and recrystallization. This simple work-up procedure is also beneficial to this method. Further applications of this catalyst to other transformations are currently under investigation.

Acknowledgment

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Supplementary data

Supplementary data (spectroscopic data for the Mannich reaction products) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.10.125.

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