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N-Heterocyclic Carbene-Catalyzed Nucleophilic Aroylation of Fluorobenzenes

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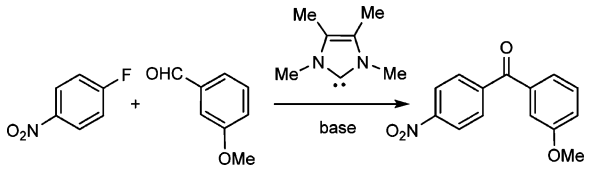
Received November 5, 2007



In N-heterocyclic carbene (NHCs) catalyzed nucleophilic substitution of fluorobenzenes, fluoro groups are replaced by aroyl groups, which are derived from aromatic aldehydes. 1,3,4,5-Tetramethylimidazol-2-ylidene is found to be an efficient catalyst. The catalyst loading can be reduced to 1 mol % without a significant decrease in the product yields. Polysubstituted benzophenones are synthesized from fluorobenzenes and benzaldehydes by the NHC-catalyzed aroylation.

N-heterocyclic carbenes (NHCs) have become an indispensable class of ligands for transition-metal catalysis because of their characteristic similarities and superiority to ubiquitous phosphine ligands.[1,2] In addition to functioning as ligands, the NHCs play an important role as organocatalysts in a number of reactions.[1,3] Besides the widely known benzoin condensation[4] and Stetter reaction,[5] the use of the NHCs as organocatalysts has recently been extended to a variety of reactions such as transesterification/amidation, living ring-opening polymerization, and homoenolate reaction.[6−9]

In our laboratory, the NHCs have been employed as catalysts for benzoin condensation,[10] retro-benzoin condensation,[11] nucleophilic substitutions,[12−15] asymmetric acylations,[16] and cyanosilylations.[17] The NHCs catalyze the nucleophilic substitution of electron-deficient haloheteroarenes,[12] *N*-phenylimidoyl chlorides,[13] and fluorobenzenes bearing electron-withdrawing groups.[14] In this nucleophilic substitution, the halogen substituents of these compounds are replaced by aroyl groups originating from

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10.1021/jo7023569 CCC: $40.75
Published on Web 02/22/2008

SCHEME 1. Nucleophilic Aroylation of 1 Previously Reported by Our Group

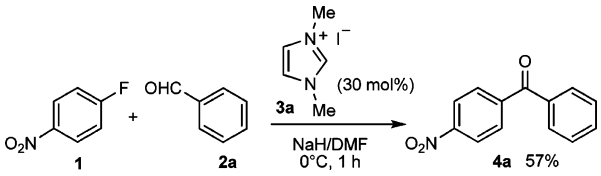
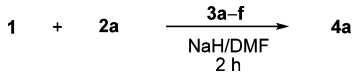


TABLE 1. Benzoylation of 1 Using 3a−f as NHC Precursors



entry	cat. (mol %)	condition[a]	yield (%)
1	**3a** (30)	A	66
2	**3b** (30)	A	45
3	**3c** (30)	A	70
4	**3d** (30)	A	76
5	**3e** (30)	A	75
6	**3f** (30)	A	quant
7	**3f** (10)	B	81
8	**3f** (1)	B	79
9	**3f** (0.5)	B	39

[a] A: −15 °C to rt. B: −15 °C, 10 min, and then to −5 to 0 °C.

aldehydes to obtain keto compounds. For example, the reaction of **1** with benzaldehyde **2a** using 30 mol % of the NHC derived from **3a** at 0 °C for 1 h in DMF affords 4-nitrobenzophenone **4a** in 57% yield (Scheme 1).[14] As shown in Scheme 2, it is considered that the reaction pathway includes the "Breslow intermediate,"[1] as in the benzoin and Stetter reactions.

SCHEME 2. Plausible Mechanism for Aroylation of 4-Fluoronitrobenzene 1

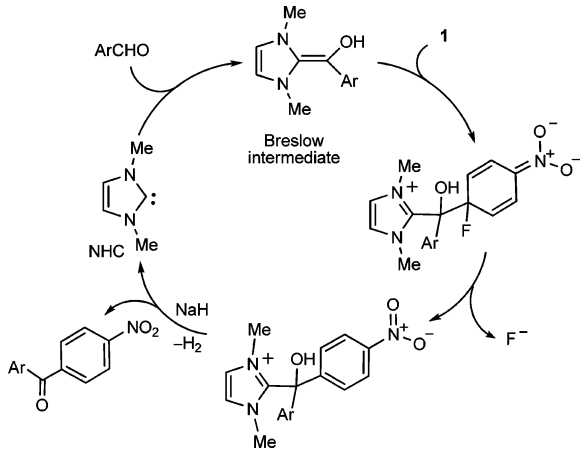
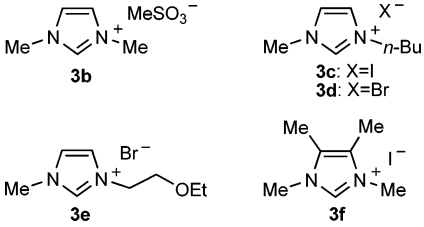
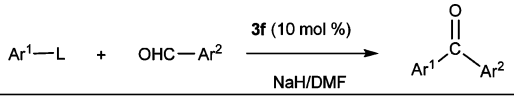


CHART 1. Imidazolium Salts 3b−f



In this study, we have examined the aroylation of fluorobenzenes using imidazolium salts with various substituents as NHC precursors to improve the yields and reduce catalyst loading.

TABLE 2. Aroylation of Benzene Derivatives 1, 5−7



entry	Ar^1 L	aldehyde (Ar^2=)	condition[a]	product	yield (%)
1	**1**	**2b**	A	**4b**	64
2	**1**	**2c**	A	**4c**	85
3	**1**	**2d**	A	**4d**	70
4	**5**	**2a**	B	**8**	53
5	**6**	**2a**	A	**4a**	8[b]
6	**7**	**2a**	A	**4a**	81

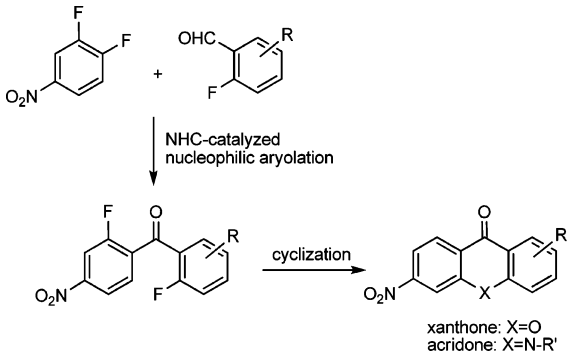
[a] A: −15 °C, 10 min, and then to 0 °C, 2 h. B: 0 °C, 10 min, rt, 30 min, and then to 80 °C, 1.5 h. [b] **8** was obtained in 10% yield.

We have also examined the synthesis of polysubstituted benzophenones from fluorobenzenes and aldehydes using the NHC-catalyzed aroylation.

The nucleophilic aryolation of **1** was examined using various imidazolium salts **3a**−**f** as the NHC precursors (Chart 1), while **3a** has been used as the NHC precursor in the nucleophilic aroylation of fluorobenzenes in the previous reports.[14,15]

The reaction with **2a** was carried out using 30 mol % of **3a** as the NHC precursor and sodium hydride at −15 °C up to room temperature in DMF (Table 1, entry 1). The NHC was generated in situ and catalyzed the reaction to obtain **4a** in 66% yield. The reactions using the other imidazolium salts were also examined under the same reaction conditions. While 1,3-dimethylimidazolium methanesulfonate **3b** afforded a lower product yield (entry 2), the use of liquid unsymmetrical imidazolium salts **3c**−**e** increased the product yields to 70−76% (entries 3−5). It was expected that the electron-donating effect of the methyl groups at C-4 and C-5 of imidazol-2-ylidene would increase the nucleophilicity of the carbene center and accelerate the reaction. In fact, the reaction in the presence of the NHC derived from 1,3,4,5-tetramethylimidazolium iodide **3f** yielded **4a** quantitatively (entry 6). When the catalyst loading was decreased to 10 mol %, the reaction using **3f** proceeded in 81% product yield (entry 7). Even with 1 mol % of **3f**, the product yield did not drop significantly, and **4a** was obtained in 79% yield under the same condition (entry 8). However, the use of 0.5 mol % of **3f** lowered the product yield (entry 9).

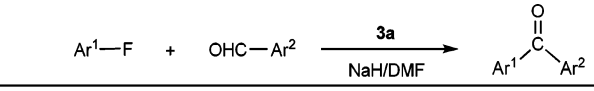
SCHEME 3. Synthesis of Xanthones and Acridones via NHC-Catalyzed Nucleophilic Aroylation

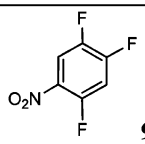
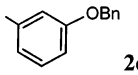
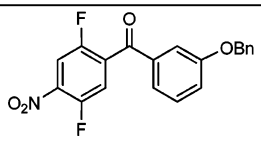
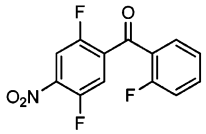
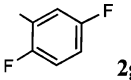
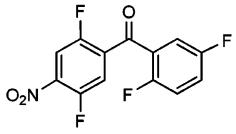
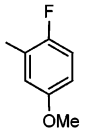
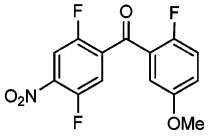
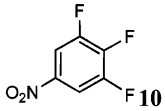
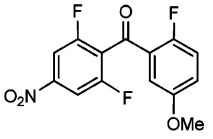


The aroylation of **1** with the other aldehydes **2b**−**d** was also carried out with 10 mol % of **3f** at −15 °C up to room temperature in DMF, and the benzophenones **4b**−**d** were obtained in good yields (Table 2, entries 1−3). The benzoylation of 4-fluorobenzophenone **5** with **2a** at 80 °C afforded **8** in 53% yield (entry 4).

Chlorobenzenes are far less susceptive to the nucleophilic aroylation as compared to fluorobenzenes. In the case of

TABLE 3. Synthesis of Polysubstituted Benzophenones 1,5−7



entry	Ar^1 F	aldehyde[a] (Ar^2=)	Cat. (mol%)	condition	product	yield (%)
1	 **9**	 **2e**	30	–15°C to r. t., overnight	 **11e**	52
2	**9**	**2e**	10[b]	–15°C, 10 min and then to –5°C, 2.5 h	**11e**	58
3	**9**	 **2f**	30	–15°C, 10 min and then to r. t., 2 h	 **11f**	71
4	**9**	 **2g**	30	–15°C, 1 h and then to r. t., 2 h	 **11g**	55
5	**9**	 **2h**	10	–15°C, 10 min and then to r. t., 2 h	 **11h**	72
6	 **10**	**2h**	10	0°C, 50 min	 **12**	89

[a] A 1 equiv portion of **2e**−**g** was used in entries 1−5, and 1.5 equiv of **2h** was used in entries 5 and 6. [b] **3f** was used instead of **3a**.

4-chloronitrobenzene **6** instead of **1**, the yield of **4a** was only 8% and 1,4-dibenzoylbenzene **8** was produced in 10% yield by the substitution of the nitro group of **4a** (entry 5). On the other hand, in the reaction of 1,4-dinitrobenzene **7** with **2a**, the nitro group underwent a smooth substitution to obtain **4a** in 81% yield (entry 6).

The synthesis of the polysubstituted benzophenones was examined. Benzophenones are versatile building blocks. For example, we have reported the synthesis of heterocyclic compounds such as xanthones and acridones from 2,2′-difluorobenzophenones that were prepared by aroylation (Scheme 3).[15]

The fluoride **9** was subjected to aroylation with the aldehydes **2e**−**h** (Table 3). Since **3a** is more readily available than **3f**, **3a** (30 mol % or 10 mol %) was used as the catalyst precursor (entries 1,3−6). The reactions were carried out at −15 °C up to the ambient temperature to obtain the polysubstituted benzophenones **11e**−**h** in 52−72% yields (entries 1,3−5). When **3f** (10 mol %) was used instead of **3a** (30 mol %) in the reaction of **9** and **2e**, **11e** was obtained in the slightly higher yield (entry 2). The aroylation of **10** with **2h** (1.5 equiv) using 10 mol % of **3a** occurred at 0 °C for 50 min to obtain **12** in good yield (89%, entry 6).

In conclusion, we have demonstrated that the NHC derived from 1,3,4,5-tetramethylimidazolium iodide is a powerful catalyst for the nucleophilic aroylation. The catalyst loading can be reduced to 1 mol % without a significant drop in the product yield of the reaction between **1** and **2a**. We have also shown that this aroylation is useful for the synthesis of polysubstituted benzophenones. This organocatalytic aroylation enables us to synthesize the benzophenones (such as **4d**, **11g**, **11h**, and **12**) that are not accessible via conventional electrophilic aroylation (Friedel−Crafts reaction). We believe that we have broadened the scope of accessible benzophenones. The applications of this reaction to the syntheses of natural products containing a xanthone nucleus are currently underway in our laboratories.

Experimental Section

Typical Prodedure for Aroylation: 4-Nitrobenzophenone (4a). Under an argon atmosphere, 60% sodium hydride in oil (160 mg, 4 mmol) was added to a mixture of 4-fluoronitrobenzene **1** (141 mg, 1 mmol), benzaldehyde **2a** (106 mg, 1 mmol), and 1,3-dimethylimidazolium iodide **3a** (22 mg, 0.1 mmol) in DMF (7 mL). The mixture was stirred at −15 °C for 15 min; then, the reaction temperature was allowed to rise to −5 °C, and the mixture was continually stirred for 2 h altogether. After the reaction, the mixture was poured into ice water. The products were extracted with ethyl acetate. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate) to obtain benzophenone **4a**. The recrystallization of the crude product from methanol yielded the crystals of **4a** in the form of slightly orange needles: mp 136−137 °C (lit.[18] 136−138 °C); IR (KBr): 1643 (CO), 1508, 1354 (NO_2) cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ 7.53 (2H, t, $J = 8$ Hz), 7.66 (1H, t, $J = 8$ Hz), 7.81 (2H, d, $J = 8$ Hz), 7.94 (2H, d, $J = 9$ Hz), 8.35 (2H, d, $J = 9$ Hz).

Supporting Information Available: Compound characterization data and copies of spectra and chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.

JO7023569

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