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The NHCs-mediated cross-coupling of aromatic aldehydes with benzyl halides: synthesis of α-aryl ketones

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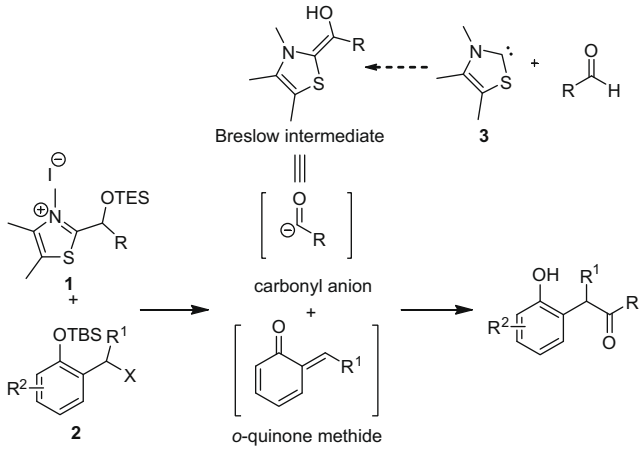
ABSTRACT

A new NHCs-mediated synthetic method was found to produce α-aryl ketones in 22–63% yields in one-pot process from the corresponding aromatic aldehydes and benzyl halides. This method is the first example of the NHCs-mediated intermolecular nucleophilic acylation of aromatic aldehydes with benzyl halides.

Umpolung reactivity of functional groups by *N*-heterocyclic carbenes (NHCs) is a powerful method for reversing the normal mode of reactivity and has been widely employed by organic chemists, including Stetter reactions,[1] Benzoin condensations,[2] Diels–Alder reactions,[3] and so on.[4] Generally speaking, the Stetter reaction is the NHCs-catalyzed addition of aldehydes to Michael acceptors (C=C—EWG) such as α,β-unsaturated carbonyl compounds, α,β-unsaturated nitriles, and nitroalkenes. To the best of our knowledge, only few reports described the NHCs-mediated C–C bond formation reactions using activated halides such as *p*-nitrofluorobenzene[5] and heteroarylchlorides[6] as electrophilic substrates instead of Michael acceptors. Interestingly, there is not a single report regarding the coupling of Breslow intermediate with benzyl halide. The main reason presumably attributes to the ammonium salt formation in situ from benzyl halide and organic base.

Recently, Scheidt and Mattson[7] reported the nucleophilic acylation of *o*-quinone methides (Scheme 1). In this strategy, stable *O*-silyl thiazolium carbinols **1** employed as Breslow intermediate equivalents of carbonyl anion reacted with *O*-silylated phenols **2**, precursors of *o*-quinone methides, to afford α-aryl ketones. Notably, *O*-silyl thiazolium carbinols **1** generated the Breslow intermediate in situ in the presence of fluoride. Furthermore, it is worth pointing out that the reaction of *O*-silyl thiazolium carbinols **1** with benzyl bromide afforded the corresponding ketone in very low yield, and the competition experiment showed that an *o*-hydroxy group or a potential *o*-hydroxy group on aromatic ring is the prerequisite for acceptor **2** to form the *o*-quinone and promote this reaction. Therefore, we are wondering whether the Breslow intermediate, generated in situ from aldehyde and NHC, can react with simple benzylic halides to afford the α-aryl ketones without presynthesizing *O*-silyl thiazolium carbinols **1**. Herein, we would like to present the first example of the NHCs-mediated intermolecular nucleophilic acylation of simple benzylic halides with aromatic aldehydes affording biologically important or synthetically useful α-aryl ketones.

Initially, benzaldehyde, benzyl bromide, and thiazolium salt **7a** were chosen to test our idea as model reaction. Unfortunately, no desired product was detected under many reaction conditions varying from solvent, base, and reaction temperature. Interestingly, when *p*-bromobenzaldehyde was employed instead of benzaldehyde for this reaction in CH_2Cl_2 at refluxing temperature with triethylamine as a base, the reaction produced the benzyl 4-bromobenzoate instead of the desired product α-aryl ketone, in 15% yield (Table 1, entry 1). When the reaction was carried out in



Scheme 1. Nucleophilic acylation of *o*-quinone methides by Scheidt.

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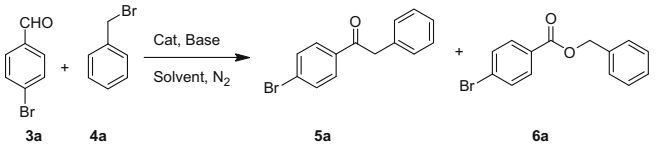
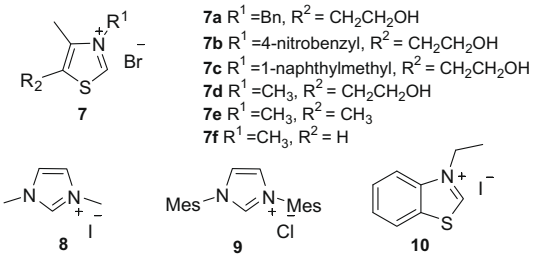
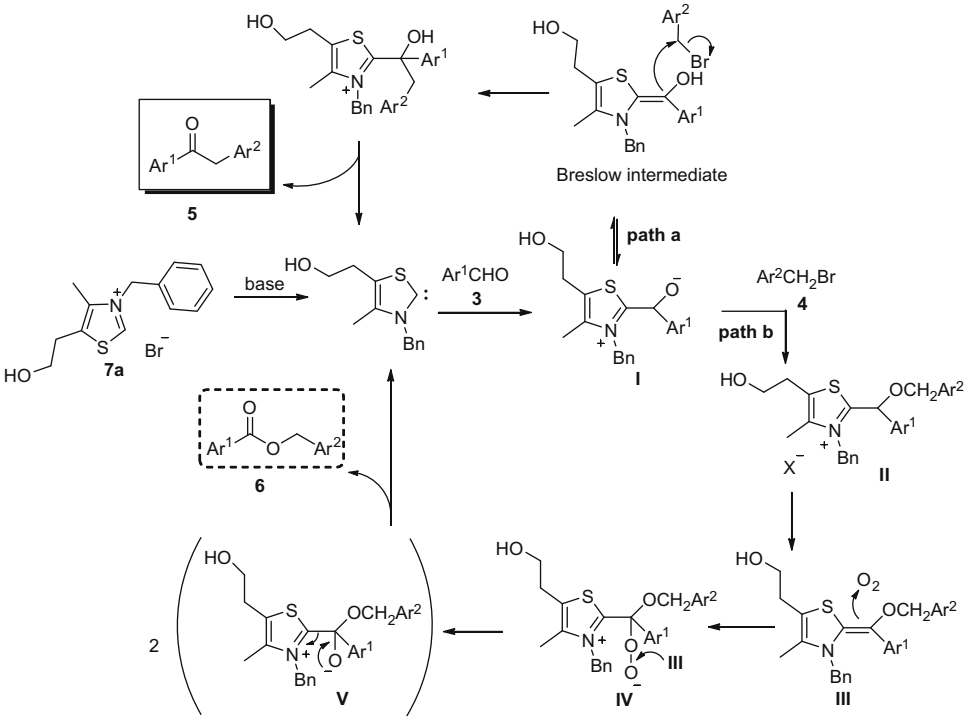
Table 1
The optimization of reaction conditions for the synthesis of α-aryl ketones[a]





Entry	Catalyst (mol %)	Base	Solvent	Yield (%) of **5a**	Yield (%) of **6a**
1	**7a** (50)[b]	TEA	CH_2Cl_2	ND	15
2	**7a** (50)[b]	TEA	CH_3CN	ND	35
3	**7a** (50)[b]	DBU	CH_3CN	ND	45
4	**7a** (50)	DBU	CH_3CN	23	17
5	**7a** (100)	DBU	CH_3CN	39	3
6	**7a** (100)	TEA	CH_3CN	ND	29
7	**7a** (100)	DABCO	CH_3CN	ND	ND
8	**7a** (100)	DBN	CH_3CN	19	6
9	**7a** (100)	DBU	DMF	20	26
10	**7a** (100)	DBU	THF	ND	ND
11	**7a** (100)	DBU	EtOH	12	ND
12	**7b** (100)	DBU	CH_3CN	ND	ND
13	**7c** (100)	DBU	CH_3CN	40	13
14	**7d** (100)	DBU	CH_3CN	42	3
15	**7e** (100)	DBU	CH_3CN	43	3
16	**7f** (100)	DBU	CH_3CN	63	5
17	**8** (100)	DBU	CH_3CN	ND	ND
18	**9** (100)	DBU	CH_3CN	ND	ND
19	**10** (100)	DBU	CH_3CN	ND	ND

[a] Reaction condition: *p*-bromobenzaldehyde (1.0 equiv), benzyl bromide (2.0 equiv), catalyst (100 mol %), base (1.25 equiv), rt, nitrogen atmosphere, 5 min.
[b] Reaction was conducted at aerobic condition, 12 h.



Scheme 2. Proposed mechanism for the NHCs-mediated cross-coupling of aromatic aldehydes with benzyl bromide.

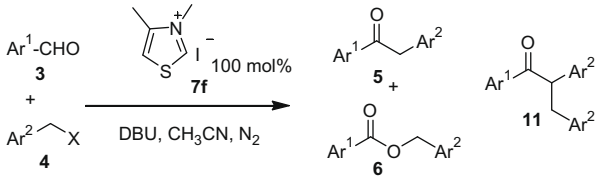
CH_3CN, using different bases such as TEA and DBU, the benzyl 4-bromobenzoate was obtained in 35% and 45% yields, respectively (entries 2 and 3), however, without the desired product α-aryl ketone. This unexpected result prompted us to further investigate the reaction mechanism. We then proposed a possible pathway accounting for the formation of the unexpected ester product through the NHCs-mediated reaction of aromatic aldehyde with benzyl bromide. As shown in Scheme 2, the intermediate **I** reacts with benzyl bromide to form a benzyl ether **II**, which isomerizes to intermediate **III** and is then subjected to an oxygen oxidation to form ester **6** after the NHC departure. It is apparent that the presence of oxygen is the key factor for generating the unexpected ester product, which is consistent with Chen's result.[8] This reaction pathway was confirmed by the synthesis of key intermediate **IIf**.[9] On the other hand, it is well known that the intermediate **I** easily isomerizes to the Breslow intermediate via path **a**, which would react directly with benzyl bromide to form the desired product α-aryl ketone **5**. If this is true, we believed that the removal of oxygen would facilitate the reaction proceeding through path **a**. Therefore, the reaction condition for the coupling of *p*-bromobenzaldehyde with benzyl bromide at oxygen-free atmosphere was further screened in order to produce the desired α-aryl ketone. The results are summarized in Table 1.

To our delight, when the reaction was conducted under nitrogen atmosphere at room temperature, the desired product ketone **5a** was obtained in 23% yield along with 17% of ester **6a** (entry 4). The yield of ketone **5a** increased to 39% surprisingly in 5 min when the amount of catalyst **7a** was increased from 50 mol % to 100 mol % (entries 4 and 5). Screening of the bases turned out that DBU was the optimal one (entries 5–8). Solvents optimization found that CH_3CN gave the best yield of ketone **5a** (entries 5 and 9–11). Screening of NHCs showed that thiazolium salt was more suitable for this reaction (entries 12–19), and thiazolium salt **7f** gave the best yield up to 63% (entry 16). Therefore, the optimal reaction condition for the production of α-aryl ketone is carried out in anhydrous acetonitrile at room temperature under nitrogen atmosphere using thiazolium salt **7f** (100 mol %) and DBU as the base.[10]

To explore the generality and scope of this reaction, representative aromatic aldehydes and various benzyl halides were examined under the above-mentioned optimal condition (Table 2). Initially, a survey of the effect of benzyl-leaving groups (Br, Cl, and OTs) showed that bromine was the most ideal leaving group and gave the highest yield of ketone **5a** up to 63% (entries 1–3). We then investigated the reactivities of four different benzylic bromides. It was found, in most cases, that benzyl bromides gave the corresponding α-aryl ketones in 22–63% yields (entries 1 and 4–7). Interestingly, 2-(bromomethyl) benzonitrile **4b** gave normal ketone **5b** in 18% yield along with a further alkylated ketone **11b** in 34% yield (entry 4). 4-Nitrobenzaldehyde surprisingly afforded the ester **6h** in 41% yield instead of the desired product ketone due to unclear reason. On the other hand, aldehydes bearing electron-donating group (EDG) on aromatic ring gave no desired products presumably due to their low reactivities (entries 12 and 13).

In conclusion, we have developed a new NHCs-mediated synthetic method[10] to produce α-aryl ketones in 22–63% of yields in one-pot process from corresponding aldehydes and benzyl halides under optimal reaction condition. In addition, this reaction interestingly afforded an unexpected benzyl ester (up to 45% yield) as major product at aerobic condition. Although, according to the proposed mechanism shown in Scheme 2, the NHC is the catalytic active species, we are still using stoichiometric amount of thiazolium salt, which is similar to Scheidt's result. This may attribute to the dimerization of active NHC species[11] and unreactive ammonium salt formation in situ from DBU and benzyl bromide.[12] Nevertheless, our strategy well complements Scheidt's method, in which benzyl bromide was barely reactive to Breslow intermediate to generate α-aryl ketones without *o*-hydroxy group. More importantly, it is the first example of the NHCs-mediated intermolecular nucleophilic acylation of aromatic aldehydes with benzyl halides. Further study focusing on the optimization and application of this umpolung process is in progress in our laboratory.

Table 2
The generality and scope of the NHCs-mediated coupling of aromatic aldehydes with benzylic halides[a]



Entry	R^1	R^2	X	Yield (%) of **5**	Yield (%) of **6**
1 (**a**)	*p*-(Br)Ph	Ph	Br	63	5
2 (**a**)	*p*-(Br)Ph	Ph	Cl	22	16
3 (**a**)	*p*-(Br)Ph	Ph	OTs	29	5
4 (**b**)	*p*-(Br)Ph	*o*-(CN)Ph	Br	18 (**5b**) 34 (**11b**)	ND
5 (**c**)	*p*-(Br)Ph	*o*-(CF_3)Ph	Br	47	ND
6 (**d**)	*p*-(Br)Ph	*p*-(Br)Ph	Br	30	ND
7 (**e**)	*p*-(Br)Ph	1-Naphthyl	Br	42	ND
8 (**f**)	*p*-(Cl)Ph	Ph	Br	50	ND
9 (**g**)	*p*-(CF_3)Ph	Ph	Br	55	ND
10 (**h**)	*p*-(NO_2)Ph	Ph	Br	ND	41
11 (**i**)	Ph	Ph	Br	34	ND
12 (**m**)	*p*-(OMe)Ph	Ph	Br	ND	ND
13 (**n**)	*p*-(NMe_2)Ph	Ph	Br	ND	ND

[a] Reaction condition: aromatic aldehydes (1.0 equiv), benzylic halides (2.0 equiv), NHC (100 mol %), DBU (1.25 equiv), rt, nitrogen atmosphere, 5 min.

Acknowledgments

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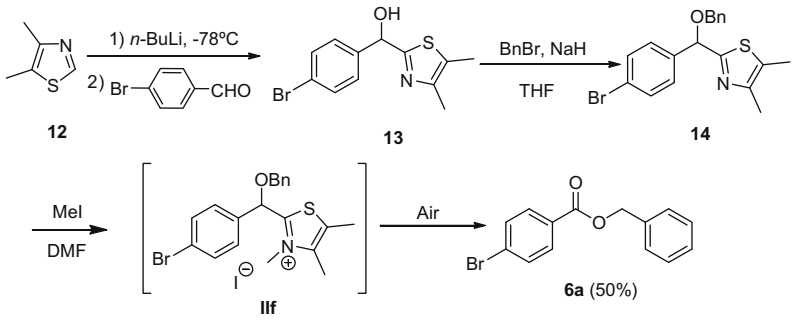
9. According to a modified procedure of Miyashita's method,[13] the benzyl ether **14** was prepared smoothly. Upon treatment with MeI in DMF, the ether **14** gave ester **6a** in 50% yield via the formation of key intermediate **IIf** and subsequent air oxidation, without generating any amount of ketone. The intermediate **IIf** was not isolated due to its chemical instability.



10. General procedure for synthesis of α-aryl ketones: To a flame-dried 25 mL schlenk tube under positive nitrogen pressure were added aromatic aldehyde **3** (0.3 mmol), benzylic halide **4** (0.6 mmol), thiazolium salt **7** (0.3 mmol), and anhydrous CH_3CN (2 mL). The resulting solution was stirred at room temperature until the thiazolium salt was completely dissolved. Then, DBU (0.375 mmol) was added and the mixture turned dark immediately. After stirring at room temperature for additional 5 min, the reaction was concentrated in vacuo and the residue was purified by column chromatography on silica gel. All products give satisfactory analytical data. The data for selected compound **5a**: Mp: 113–115 °C (lit[14] mp 112–113 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 8.7 Hz, 2H), 7.62 (d, J = 8.7 Hz, 2H), 7.39–7.33 (m, 2H), 7.30–7.27 (m, 3H), 4.27 (s, 2H). Compound **6a**: (lit[15]) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 8.6 Hz, 2H), 7.61 (d, J = 8.6 Hz, 2H), 7.49–7.37 (m, 5H), 5.39 (s, 2H).
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12. There was only trace amount of ketone formed, when the benzyl bromide (2.0 equiv) was mixed with DBU (3.0 equiv) in acetonitrile for half an hour until the complete ammonium formation, then aldehyde (1.0 equiv) and thiazolium salt (1.0 equiv) were added into the above-mentioned mixture, and the resulting mixture was stirred at room temperature for 2 h.
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