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Selective transition metal-free aroylation of diarylmethanes with 2-acyl-imidazolium salts *via* acyl C–C bond cleavage

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Introduction

Among the α -aryl carbonyl compounds, 1,2-diaryl- and 1,2,2triarylethanones have gained considerable attention because of their widespread abundance in numerous bioactive compounds¹ and natural products.² The most popular route for the synthesis of these privileged carbonyl compounds utilizes the palladium-catalyzed α arylation of ketone enolates, an approach pioneered simultaneously by Buchwald, Hartwig, and Miura in 1997 (Scheme 1A).³ Subsequently, this methodology has been expanded to involve cheaper metals such as nickel,⁴ copper,⁵ and iron.⁶ To avoid the employment of precious and toxic metals, Taillefer and co-workers recently developed a transition metal-free method.⁷ However, the substrate scope was limited and only aryl iodides worked well in most cases.

On the other hand, the development of new methods for the cleavage and formation of C-C bonds remains challenging.8 Over the past decades, a series of groundbreaking transition metalinvolved strategies have been developed in this area.⁹ Of these, acyl C(O)-C bond cleavage has attracted significant interest in organic synthesis.¹⁰ From an acylation viewpoint, there have been numerous advances in the transition metal-catalyzed cross-coupling reactions of amides and aromatic esters via C(O)-N and C(O)-C cleavage.^{11,12} Apart from cleaving the more polarized C(O)–N and C(O)–C bonds, reactions proceeding via direct activation of the less polarized acyl C(O)-C bond are scarce and remains a challenge to date.¹³ To facilitate C-C bond cleavage, the conversion of various functional groups into their salts represents an alternative strategy due to their improved leaving ability. Accordingly, several groups have utilized 2-acyl-imidazolium salts for amidation and esterification via acyl C(O)-C bond cleavage.¹⁴ In this context, we were curious if 2-acylimidazolium salts could be employed with other nucleophiles. Recently, we reported the synthesis of 1,2,2-triarylethanones via the aroylation of diarylmethanes with amides under metal-free

ABSTRACT

A highly chemoselective method is reported for the aroylation of simple diarylmethane derivatives *via* direct acyl C–C cleavage with 2-acyl-imidazolium salts under transition metal-free conditions. This represents a straightforward way to access a variety of sterically and electronically diverse 1,2,2-triarylethanones, a class of compounds with biological activities and various applications.

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conditions (Scheme 1B).¹⁵ Diarylmethane is weakly acidic.¹⁶ These benzylic C–H bonds can be reversibly deprotonated under basic reaction conditions (MN(SiMe₃)₂, M = Li, Na, K), and the resulting carbanions act as nucleophiles in transition metal-involved¹⁷ or transition metal-free transformations.¹⁸ For the current study, we were interested in alternative strategies to prepare the same 1,2,2triarylethanones *via* the aroylation of diarylmethanes with 2-acylimidazolium salts (Scheme 1C). There are several features of our study that should be noted: (a) 2-acyl-imidazolium salts are easy to prepare; (b) high functional group tolerance (ketones, halides, esters); (c) expensive and toxic organometallic reagents are avoided.

Scheme 1. Representative methods for the synthesis of 1,2,2-triarylethanones.





B. Aroylation of diarylmethanes with amides under metal free conditions



Results and Discussion

We commenced our exploration by examining the model reaction of 2-benzoyl-1,3-dimethyl-1*H*-imidazol-3-ium iodide **1a** with 4benzylpyridine **2a** in THF using NaN(SiMe₃)₂ as a base. After heating at 80 °C for 12 h, the desired product **3aa** was formed in 48% isolated yield. The screening of five bases indicated that silyl amide bases were suitable for this transformation (Entries 1–3), with LiHMDS the most promising (78% yield). Other bases, such as NaO'Bu and KO'Bu, failed to give the product (Entries 4–5). Various solvents (DME, THF, CPME (cyclopentyl methyl ether), 1,4-dioxane and toluene) were next explored, where DME was found to be the best choice, and toluene also provided an acceptable yield (Entries 6–9). The temperature dramatically affected the yields; only 44% yield was observed when the reaction temperature was lowered to 60 °C, and no product was observed at 40 °C (Entries 10–11).

Table 1. Optimization of the reaction conditions.^a

Ĺ		3 ec solv	uiv base ent, 80 °C	N N
Entry	Base	Solvent	Temp. (°C)	Jaa Yield 3aa ^b
1	NaHMDS	THF	80	48
2	KHMDS	THF	80	39
3	LiHMDS	THF	80	76
4	NaO'Bu	THF	80	0
5	KO'Bu	THF	80	0
6	LiHMDS	1,4-dioxane	80	trace
7	LiHMDS	toluene	80	70
8	LiHMDS	DME	80	88
9	LiHMDS	CPME	80	trace
10	LiHMDS	DME	60	44
11	LiHMDS	DME	40	trace

^{*a*}Reagents and conditions: **1a** (0.1 mmol), **2a** (0.1 mmol), base (0.3 mmol), solvent (1 mL), 12 h. ^{*b*}Isolated yield.

After establishing the optimal reaction conditions, we next examined the scope of the diarylmethanes in this transformation. As shown in Table 2, substrates bearing electronically-diverse substituents on the phenyl group of 4-benzylpyridine (2-Me, 3-Me, 4-Me, 4-Bu, 4-OMe, 4-F) gave the desired products (**3ab**, **3ac**, **3ad**, **3ae**, **3af**, **3ag**) in 82–93% yield. Notably, the sterically-hindered substrate **2b** was tolerated in this protocol, affording the desired product in high yield (92%). Perhaps most attractive feature of this approach is the facile aroylation of diarylmethanes with privileged heterocyclic motifs, including both electron-deficient heterocycles, such as pyridine (**2i**), and electron-rich heterocycles, such as furan (**2j**, **2k**, **2l**, **2m**), as well as benzofuran (**2o**). Additionally, both fluorene (**2p**, **2q**) and benzofluorene (**2r**) proved to be suitable substrates, with the desired products isolated in 83–90% yield.

Table 2. Scope of the diarylmethane.^{*a,b*}



3aq 85%^{d,e} 3ar 83%^{d,e}

^{*a*}Reagents and conditions: **1a** (0.1 mmol), diarylmethane (0.1 mmol), LiHMDS (0.3 mmol), DME (0.1 M), 80 °C, 12 h. ^{*b*}Isolated yield. ^{*c*}KHMDS (3 equiv.). ^{*d*}NaHMDS (3 equiv.). ^{*e*}Reaction conducted in THF.

The scope of the aroylation with respect to the 2-acylimidazolium salts was next investigated with 4-benzylpyridine 2a. Replacement of the phenyl group in 2-acyl-imidazolium salt 1a with 4-biphenyl and 2-naphthyl groups worked well in this transformation, affording the corresponding products 3ba and 3ca in 75% and 85% yield, respectively. 2-Acyl-imidazolium salts bearing alkyl substituents at the meta- and para-positions gave the desired products 3da, 3ea and 3fa in 72-92% yield. Moreover, substrates possessing electronically varied substituents (2g, 2h, 2i, 2j), as well as steric hindrance (2k), were all well-tolerated. In particular, 2-acylimidazolium salts possessing halides (1g and 1h) gave the expected products in good yields (72-83%) with the carbon-halide bond remaining intact. Further functionalization of these products could be achieved through cross-coupling strategies. Furthermore, heterocyclic 2-acyl-imidazolium salts possessing furan and thiophene groups were both compatible, giving **3la** and **3ma** in 63% and 52% yield respectively.

To determine the practicality of this aroylation method, the reaction using 2-acyl-imidazolium salt **1a** with 4-benzylpyridine was performed on a 4 mmol scale. The expected product was isolated in 75% yield (0.82 g).

Table 3. Scope of the 2-acyl-imidazolium salts.^{a,b}



3ma 52%^d ^aReagents and conditions: 2-acyl-imidazolium salt (0.1 mmol), 2a (0.1

mmol), LiHMDS (0.3 mmol), DME (0.1 M), 80°C, 12 h. ^bIsolated yield. ^cKHMDS (3 equiv.). ^dNaHMDS (3 equiv.). ^eReaction conducted in THF.

Conclusion

In summary, a novel method was developed for the aroylation of diarylmethanes with 2-acyl-imidazolium salts under transition metal-free conditions. This protocol is distinct from metalcatalyzed α -arylation methods. An attractive feature of this method is its avoidance of the use of expensive and toxic metals. Further studies toward the development of new approaches involving the cleavage of C(O)–C bonds under transition metalfree conditions are currently under way.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary Material

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Highlights

- Transition metal-free aroylation of diarylmethanes with 2-acyl-imidazoliums was reported.
- 2. The method expands the application of 2-acylimidazoliums in organic synthesis.
- 3. A series of 1,2,2-triarylethanones were prepared using the method present in this study/