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Synthesis of Functionalized Imidazolium Salts via Iodine-Mediated Annulations of Enamines

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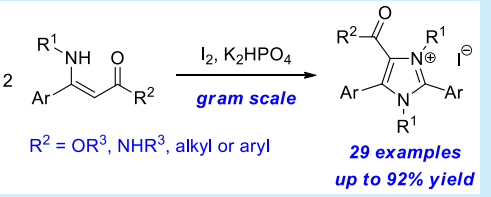
Supporting Information

ABSTRACT: A novel annulation reaction of two enamine molecules with iodine under basic conditions to form 4-functionalized imidazolium salts has been established. In this reaction, iodine acts as both an iodinating reagent and a Lewis acid catalyst. Features of this synthetic method include facilitative preparation of substrates, no use of transition metals, mild reaction conditions, simplicity of operation, and gram scale synthesis.

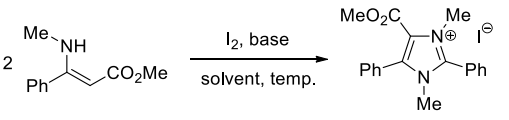


Imidazolium salts are ionic liquids (IL)[1] that have been well investigated and are valuable precursors for the preparation of *N*-heterocyclic carbenes (NHC).[2] They enjoy a wide range of applications as liquid crystals,[3] pharmaceuticals,[1c,4] and motifs of functional materials.[4c,5] To date, the construction of the heterocyclic framework of imidazolium salts uses *N*-quaternization of preformed imidazoles,[6] and Arduengo-type cyclization and variations of this reaction.[6a,7] In 2011, Polyakova and coworkers reported a modular approach to the synthesis of *N*,*N*′-di-*tert*-alkyl imidazolium salts from but-3-yn-2-yl methanesulfonates or *N*-*tert*-alkyl aldonitrones.[8] In 2013, Baslé and Mauduit devised a multicomponent cyclization reaction for the assembly of unsymmetrical imidazolium salts from sterically congested amines.[9] In 2015, the Zhu group implemented the synthesis of 1,3,4,5-tetrasubstituted imidazolium compounds from propargylamines and isonitriles in the presence of multiple combined catalysts.[10] In 2017, Su and Liu developed a gold-catalyzed [2 + 2+1] annulation reaction of aryldiazo nitriles and imines to prepare all aryl-substituted imidazolium salts.[11] Despite these elegant methods, however, novel and simple synthetic pathways to access imidazolium frameworks are still in demand.

Over the past decades, enamines have been shown to play an important role in organocatalysis[12] and have also been used extensively for the synthesis of diverse heterocyclic compounds[13] including indoles,[14] pyridines,[15] pyrroles,[16] pyrazoles,[17] and imidazoles.[18] However, to the best of our knowledge, annulation reactions of enamines to form imidazolium skeletons have never been investigated. In this paper, we demonstrate such a reaction for the synthesis of 4-functionalized 1*H*-imidazol-3-ium salts from readily accessible enamines, a reaction promoted by molecular iodine under basic conditions.

The required enamine substrates can be readily obtained by the condensation of aliphatic amines with *β*-keto esters. In the presence of a base such as K_2CO_3, the I_2-mediated annulation of two enamine molecules (**1a**) forms 2,5-diphenyl-1*H*-imidazol-3-ium iodide salt (**2a**) in 1,2-dichloroethane (DCE) at 50 °C, the optimal reaction temperature (Table 1, entry 2). Solvent

Table 1. Optimization of Reaction Conditions[a]



1a **2a**

entry	base	solvent	temp	time	yield[b]
1	K_2CO_3	DCE	rt	8 h	54%
2	K_2CO_3	DCE	50 °C	4 h	73%
3	K_2CO_3	DCE	84 °C	4 h	34%
4	K_2CO_3	toluene	50 °C	4 h	69%
5	K_2CO_3	CH_2Cl_2	40 °C	4 h	36%
6	K_2CO_3	$CHCl_3$	50 °C	8 h	54%
7	K_2CO_3	CCl_4	50 °C	6 h	65%
8	K_2CO_3	DMSO	50 °C	1 h	0%
9	K_2CO_3	MeOH	50 °C	1 h	0%
10	Li_2CO_3	DCE	50 °C	4 h	22%
11	K_2HPO_4	DCE	50 °C	4 h	86% (82%)[c]
12	K_3PO_4	DCE	50 °C	4 h	55%
13	LiOH	DCE	50 °C	4 h	31%
14	NaOH	DCE	50 °C	1 h	trace
15	$NaHCO_3$	DCE	50 °C	4 h	0%
16	NaOAc	DCE	50 °C	6 h	23%
17	^{t}BuOK	DCE	50 °C	8 h	20%
18	LiHMDS	DCE	50 °C	2 h	trace
19	DBU	DCE	50 °C	1 h	0%
20[d]	K_2HPO_4	DCE	50 °C	4 h	82%
21[e]	K_2HPO_4	DCE	50 °C	4 h	79%

[a]Optimal reaction conditions (entry 11): **1a** (0.5 mmol), I_2 (0.65 mmol), K_2HPO_4 (1.5 mmol), DCE (10 mL), 50 °C. [b]Isolated yields. [c]Yield of gram-scale reaction (6 mmol). [d]1.5 equiv of I_2 was used. [e]With 1.5 equiv of TEMPO.

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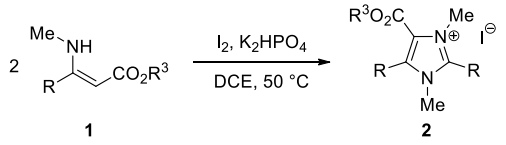
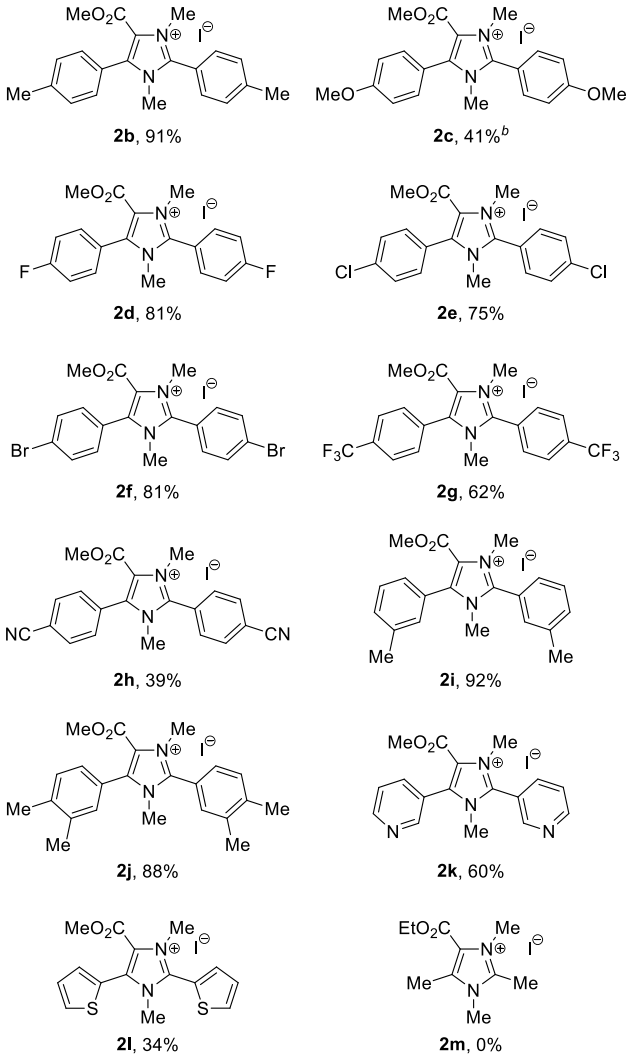
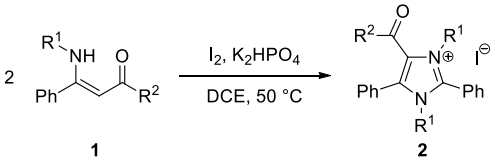
Scheme 1. Scope of R Group[a]

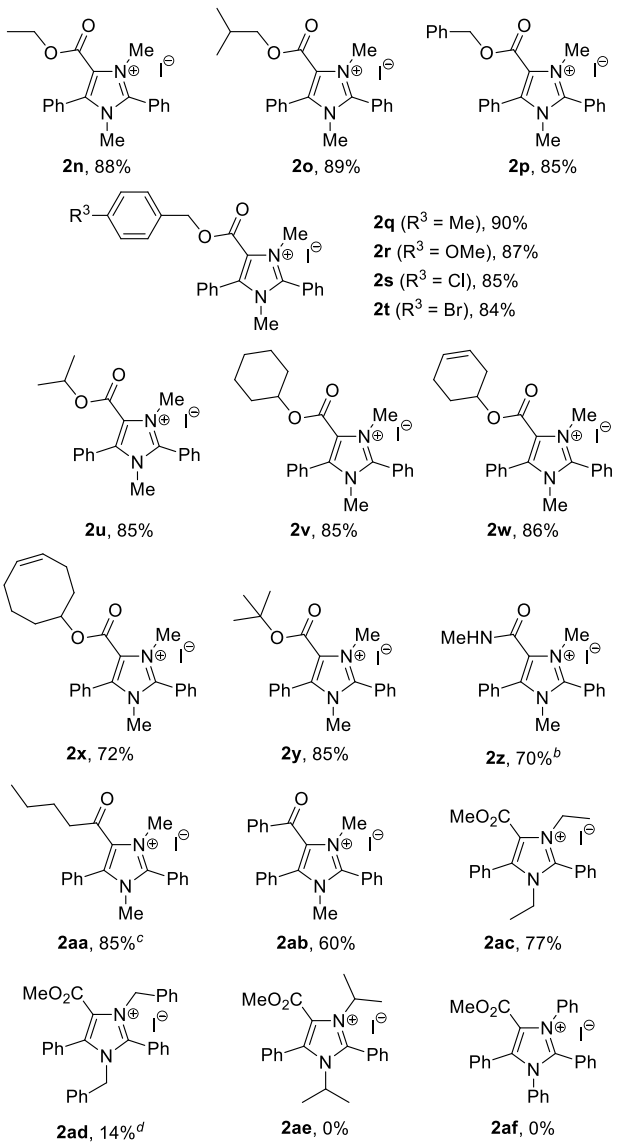




[a]Reaction conditions: **1** (0.5 mmol), I_2 (0.65 mmol), K_2HPO_4 (1.5 mmol), DCE (10 mL), 50 °C (isolated yields are given). [b]K_2CO_3 was used as base.

Scheme 2. Scope of R^1 and R^2 Groups[a]





[a]Reaction conditions: **1** (0.5 mmol), I_2 (0.65 mmol), K_2HPO_4 (1.5 mmol), DCE (10 mL), 50 °C (isolated yields are given). [b]Reaction was performed at −20 °C. [c]Reaction was performed at room temperature. [d]K_2CO_3 was used as base.

screening (entries 2, 4−9) shows that DCE is the ideal solvent for this transformation. Further screening of a series of inorganic and organic bases (entries 10−19) reveals that K_2HPO_4 is the best base (entry 11). Upon changing the base from K_2CO_3 to K_2HPO_4, the reaction also proceeds well at room temperature, but overall the yields are slightly decreased when exploring the substrate scope. Thus, 50 °C was chosen as the optimal temperature. The present reaction requires at least 1.3 equiv of iodine, and additional iodine fails to improve the yield of the product (entry 20). In addition, the product **2a** can be successfully synthesized on a gram scale (entry 11). In the presence of TEMPO, a free radical scavenger, the reaction was not affected significantly (entry 21), which ruled out a radical mechanism.

In an examination of the scope and generality of the reaction (Scheme 1), various 3-aryl enamines were subjected to the above optimal annulation conditions. Iodine-mediated cyclization of these substrates afforded the expected 4-carboxylic ester-substituted imidazolium salts in moderate to excellent yields (**2a−2l**, 34−92%). The structure of the imidazolium iodide salt (**2f**) was confirmed by X-ray crystallography.[19] This reaction is compatible with both electron-donating groups (EDGs) and electron-withdrawing groups (EWGs) on the phenyl ring (R). Generally, incorporation of EDGs favors this transformation (**2b**, **2i−2j** vs **2d−2h**). The exception is the methoxy substrate,

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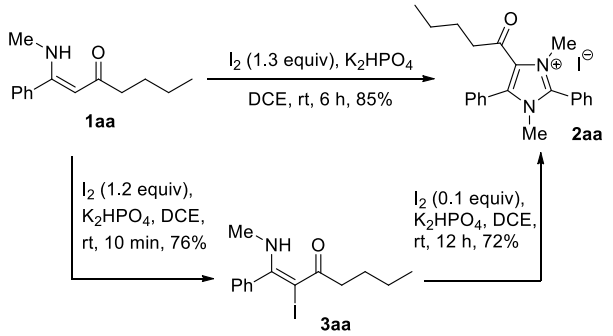
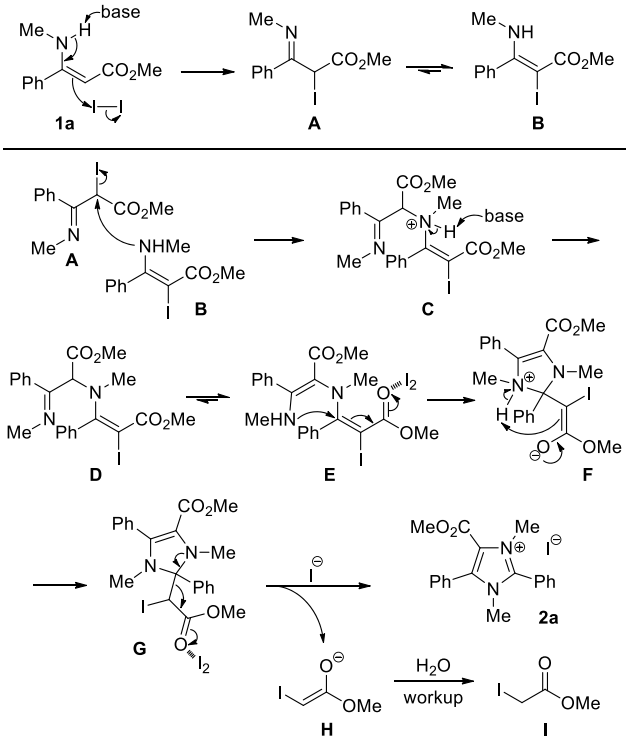
Scheme 3. Synthesis of Imidazolium Salt 2aa via Isolated Iodide 3aa



Scheme 4. Proposed Mechanism



which afforded product **2c**[20] in a decreased yield with unidentified byproducts. The reaction of an *o*-tolyl enamine resulted in complicated product mixtures,[21] which probably arose from the steric hindrance of the *ortho*-methyl group. The presence of a methoxy or a cyano substituent significantly decreases the yield of the product (**2c**, **2h**). This methodology is also successful with pyridyl and thiophenyl substituted substrates (**2k**−**2l**) but fails with an enamine bearing an alkyl group at R position (**2m**).

In light of these encouraging results, we further explored the substrate scope of enamines bearing various R^1 or R^2 groups (Scheme 2). Under the optimal reaction conditions, imidazolium salts bearing a variety of 4-functional groups (CO-R^2) (**2n**−**2ab**) are synthesized smoothly from the corresponding substrates in satisfactory yields. Replacement of the *N*-methyl group with an ethyl or benzyl group (R^1) also leads to the desired product (**2ac**−**2ad**[20]). However, in the cases of enamines **1ae**−**1af**, no expected products were formed due to the steric hindrance of the *N*-isopropyl and phenyl moieties.

Control experiments were performed to investigate the mechanism of the formation of the imidazolium entity. The iodide intermediate **3aa** could be isolated because of its relatively superior stability. Treatment of this iodide with a catalytic amount of iodine afforded the corresponding imidazolium salt (**2aa**) successfully (Scheme 3). On the basis of these experimental results and our previous works,[22] a tentative mechanism is proposed for this reaction (Scheme 4). With the reaction leading to product **2a** as an example, iodine-mediated oxidative iodination of enamine **1a** under basic conditions generates two iodides, **A** and **B**.[22] Then nucleophilic substitution of iodide **A** by the enamine nitrogen of compound **B** produces **C**, deprotonation of which forms an intermediate **D**, which furnishes compound **E** upon imine-enamine tautomerization. Subsequently, I_2-catalyzed intramolecular aza-Michael addition of **E** leads to the 2,3-dihydro-1*H*-imidazole (**G**). Finally, I_2-catalyzed rearrangement of **G** produces the imidazolium framework (**2a**) and an enolate **H**. Upon workup with aqueous solution, **H** is converted to the acetate ester (**I**).[23] In this transformation, molecular iodine plays a dual role: as an oxidant in the first step oxidative iodination, and then as a Lewis acid[24] in aza-Michael addition (**E** → **F**) and arrangement (**F** → **G**) steps, respectively.

For the first time, we have established a novel synthetic process for the construction of the imidazolium framework via I_2-promoted annulations of enamines in the presence of base. Under mild reaction conditions, cyclization of readily accessible enamine substrates affords a variety of 4-functionalized imidazolium iodide salts. In this transformation, iodine behaves as both iodinating reagent and Lewis acid catalyst. This transition-metal-free synthetic process is operationally simple and can be conveniently conducted on a gram scale.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00541.

Experimental details, characterization data, NMR spectra of isolated compounds (PDF)

Accession Codes

CCDC 1895252 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(19) CCDC 1895252 (**1f**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

(20) Under the standard reaction conditions, only 25% yield of **2c** and a trace amount of **2ad** were formed. Switching the base from K_2HPO_4 to K_2CO_3 resulted in better yields of the corresponding products as indicated in Schemes 1 and 2, respectively.

(21) The expected product has been detected by HRMS. (ESI-TOF) *m*/*z*: $[M - I]^+$ calcd for $C_{21}H_{23}N_2O_2$ 335.1754, found 335.1751. However, no pure imidazolium iodide was isolated from the complicated product mixtures.

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(23) The intermediate **H** or **I** was not detected probably due to their instability. For a similar pathway to lead an aldehyde/ketone, see: Kivrak, A.; Zora, M. A novel synthesis of 1,2,4-oxadiazoles and isoxazoles. *Tetrahedron* **2014**, *70*, 817−831.

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