Organic LETTERS

Letter

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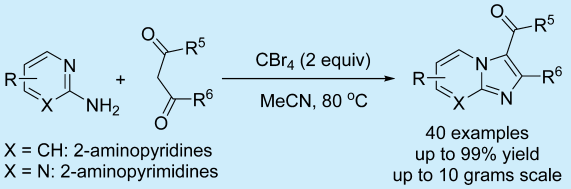
CBr_4 Mediated Oxidative C–N Bond Formation: Applied in the Synthesis of Imidazo[1,2-α]pyridines and Imidazo[1,2-α]pyrimidines

Congde Huo,* Jing Tang, Haisheng Xie, Yajun Wang, and Jie Dong

Key Laboratory of Eco-Environment-Related Polymer Materials Ministry of Education, College of Chemistry and Chemical Engineering, Northwest Normal University, Lanzhou, Gansu 730070, China

Supporting Information

ABSTRACT: The carbon tetrabromide mediated oxidative carbon–nitrogen bond formation of 2-aminopyridines or 2-aminopyrimidines with β-keto esters or 1,3-diones, leading to a variety of complex imidazo[1,2-α]pyridines or imidazo[1,2-α]pyrimidines, is reported. The reactions were realized under mild and metal-free conditions.



The formation of carbon–nitrogen bonds continues to be an active and challenging field of heterocyclic chemistry. Imidazo[1,2-*a*]pyridines (IPYs) are an important type of heterocycles and have attracted much attention due to their remarkable biological and pharmacological activities.[1] Within the IPY family, commercially available drugs have been derived, including alpidem (anxiolytic),[2] zolpidem (insomnia),[3] necopidem (anxiolytic),[4] saripidem (anxiolytic),[5] and zolimidine (antiulcer)[6] (Scheme 1, part A). In addition, molecules with the IPY moiety are also broadly applied in organometallic chemistry and material science because of their structural characteristics.[7] Not surprisingly, because of their applications in a variety of fields, many synthetic methods have been developed for IPYs. Although the preparation of these compounds has been investigated for more than a century, the past decade has witnessed a remarkable advancement in the synthesis of IPYs.[8] Among a variety of new synthetic transformations, transition-metal-catalyzed reactions have proven to be a powerful tool for the synthesis of IPY derivatives.[9] Very recently, TBAI/BF_3Et_2O/TBHP[10] or Fe/I_2/O_2[11] -catalyzed oxidative coupling of the C–N bond has been developed for the construction of IPYs (Scheme 1, part B). Although elegant processes have been reported, the development of new routes is still highly desirable for the synthesis of functionalized IPYs from readily available precursors without the necessity for prefunctionalities under simple metal-free conditions. Since 2015, carbon tetrabromide (CBr_4) has been found to show good reactivity in cross-dehydrogenative coupling (CDC) reactions to construct carbon–carbon bonds by us (Scheme 1, part C).[12] Herein, we developed a new and facile CBr_4-promoted protocol to construct structurally sophisticated IPY derivatives from readily accessible starting materials in a single operation under mild conditions (Scheme 1, part D).

As part of our continuing interest in CBr_4 assisted transformation, we wanted to attempt the CBr_4 mediated C–N bond formation reaction. The study was initiated by investigating the reaction of 2-aminopyridine **1a** with ethyl 2-benzoylacetate **2a** in the presence of 2 equiv of CBr_4. To our delight, as shown in Table 1, when the mixture was heated at 80

Scheme 1. Related Background

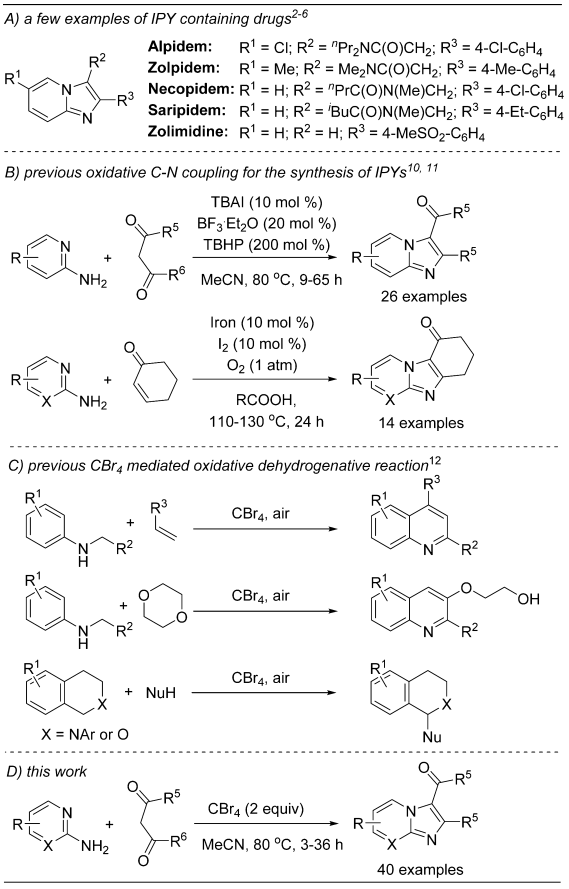


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Table 1. Screening of Reaction Conditions[a]

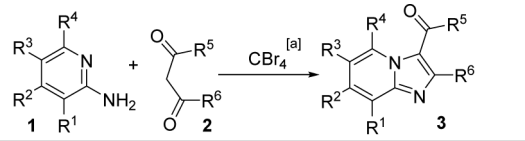
entry	[Hal]	loading	solvent	temp	yield [%][b]
1	CBr_4	2 equiv	MeCN	80 °C	90
2	NCS	2 equiv	MeCN	80 °C	60
3	NBS	2 equiv	MeCN	80 °C	62
4	NIS	2 equiv	MeCN	80 °C	40
5	DBDMH	2 equiv	MeCN	80 °C	32
6	Br_2	2 equiv	MeCN	80 °C	44
7	$CHBr_3$	2 equiv	MeCN	80 °C	trace
8	CH_2Br_2	2 equiv	MeCN	80 °C	0
9	DBE	2 equiv	MeCN	80 °C	0
10	$CuBr_2$	2 equiv	MeCN	80 °C	0
11	KBr/H_2O_2	2 equiv	MeCN	80 °C	trace
12	CBr_4	1 equiv	MeCN	80 °C	83
13	CBr_4	0.5 equiv	MeCN	80 °C	43
14	CBr_4	3 equiv	MeCN	80 °C	89
15	CBr_4	2 equiv	CH_2Cl_2	80 °C	42
16	CBr_4	2 equiv	THF	80 °C	26
17	CBr_4	2 equiv	toluene	80 °C	17
18	CBr_4	2 equiv	H_2O	80 °C	77
19	CBr_4	2 equiv	MeOH	80 °C	53
20	CBr_4	2 equiv	MeCN	60 °C	87
21	CBr_4	2 equiv	MeCN	100 °C	88
22	CBr_4	2 equiv	MeCN	rt	50

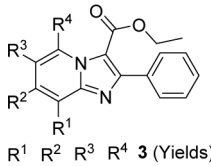
[a]Reaction conditions: **1a** (1.5 mmol), **2a** (0.5 mmol), solvent (2 mL), 6 h. [b]Yields of the isolated product. NCS = *N*-Chlorosuccinimide. NBS = *N*-Bromosuccinimide. NIS = *N*-Iodosuccinimide. DBDMH = 1,3-dibromo-5,5-dimethylhydantoin. DBE = dibromoethane.

°C for 6 h, the desired product **3aa** was isolated in excellent yield (Table 1, entry 1). The use of other halogen analogues such as NCS, NBS, NIS, DBDMH, and Br_2, instead of CBr_4, was found to be less effective (Table 1, entries 2–6). $BrCH_2CH_2Br$, $CHBr_3$, CH_2Br_2, $CuBr_2$, and KBr/H_2O_2 were inactive for this transformation (Table 1, entries 7–11). The yields dropped to 83% and 43% when the CBr_4 loading was reduced to 1 and 0.5 equiv, respectively (Table 1, entries 12, 13). Increasing the amount of CBr_4 from 2 to 3 equiv resulted in no appreciable differences (Table 1, entry 14). Furthermore, the use of other solvents such as DCM (42%), THF (26%), toluene (17%), water (77%), and MeOH (53%) was found to be less productive than MeCN (Table 1, entries 15–19). Both increasing and decreasing the temperature resulted in lower yields (Table 1, entries 20–22). Thus, it was determined that CBr_4 (2 equiv) at 80 °C in acetonitrile were the optimal reaction conditions (90%, Table 1, entry 1).

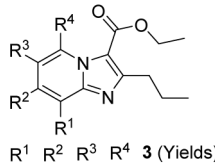
With the optimized conditions in hand, we applied this strategy to the oxidative C–N bond formation of various 2-aminopyridines **1** with different *β*-keto esters or 1,3-diones substrates **2**. As shown in Scheme 2, the reactivity of 2-aminopyridine **1** was remarkably dependent on the electronic properties of the substituents from the pyridine ring. 2-Aminopyridines without a substituent group or with an electron-donating group such as Me provided higher yields of IPYs, but 2-aminopyridines with an electron-withdrawing group such as Cl gave lower yields. Intriguingly, 2-aminopyrimidine (**1i**, a guanidine surrogate) smoothly underwent this transformation generating the desired products **3ia**–**3ih** in moderate

Scheme 2. CBr_4 Mediated Syntheses of Imidazo[1,2-*α*]pyridines and Imidazo[1,2-*α*]pyrimidines[a]

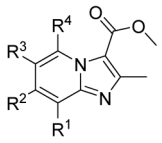




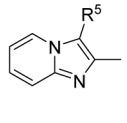
R^1	R^2	R^3	R^4	**3** (Yields)[b]
H	H	H	H	**3aa** (90%)
Me	H	H	H	**3ba** (95%)
H	Me	H	H	**3ca** (99%)
H	H	Me	H	**3da** (98%)
Cl	H	H	H	**3fa** (23%)
H	Cl	H	H	**3ga** (41%)
H	H	Cl	H	**3ha** (25%)



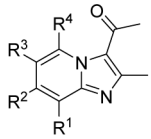
R^1	R^2	R^3	R^4	**3** (Yields)
H	H	H	H	**3ab** (88%)
Me	H	H	H	**3bb** (92%)
H	Me	H	H	**3cb** (94%)
H	H	Me	H	**3db** (95%)
H	H	H	Me	**3eb** (61%)
H	Cl	H	H	**3gb** (52%)
H	H	Cl	H	**3hb** (24 %)



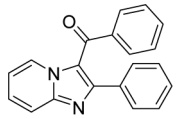
R^1	R^2	R^3	R^4	**3** (Yields)
H	H	H	H	**3ac** (90%)
Me	H	H	H	**3bc** (90%)
H	Me	H	H	**3cc** (92%)
H	H	Me	H	**3dc** (96%)
H	Cl	H	H	**3gc** (61%)
H	H	Cl	H	**3hc** (30 %)



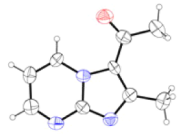
R^5	**3** (Yields)
CO_2Me	**3ac** (90%)
CO_2Et	**3ad** (89%)
$CO_2{}^iPr$	**3ae** (87%)
$CO_2{}^tBu$	**3af** (85%)



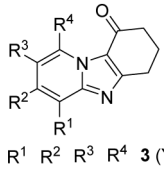
R^1	R^2	R^3	R^4	**3** (Yields)
H	H	H	H	**3ag** (89%)
Me	H	H	H	**3bg** (85%)
H	Me	H	H	**3cg** (85%)
H	H	Me	H	**3dg** (92%)
H	Cl	H	H	**3gg** (54%)



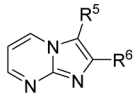
3ah (25%)



3ig



R^1	R^2	R^3	R^4	**3** (Yields)
H	H	H	H	**3ai** (36%)
Cl	H	H	H	**3fi** (32%)
H	Cl	H	H	**3gi** (33%)



R^5	R^6	**3** (Yields)
CO_2Et	Ph	**3ia** (51%)
CO_2Et	^nPr	**3ib** (58%)
CO_2Et	Me	**3id** (62%)
$CO_2{}^iPr$	Me	**3ie** (48%)
$CO_2{}^tBu$	Me	**3if** (54%)
COMe	Me	**3ig** (58%)
COPh	Ph	**3ih** (33%)

[a]Reaction conditions: **1** (1.5 mmol), **2** (0.5 mmol), MeCN (2 mL), 80 °C, 3–36 h. [b]Yield of the isolated product.

to good yields. The structure of **3ig** was confirmed by single crystal X-ray diffraction as shown in Scheme 2.[13] It is noteworthy that these imidazo[1,2-*α*]pyrimidine products were also widely applied in the synthesis of biologically active heterocycles.[14]

To examine the scalability of the present methodology, a reaction of 2-aminopyridine **1a** and ethyl 2-benzoylacetate **2a** was performed at the 10 g scale. The corresponding **3aa** was

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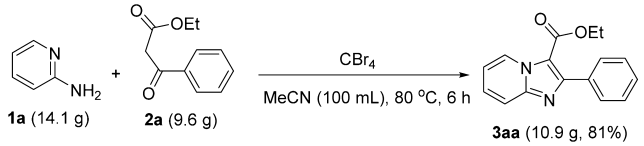
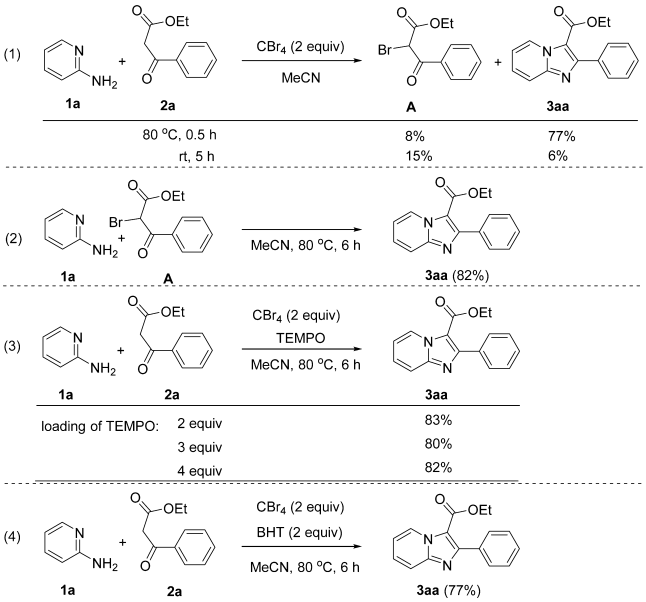
obtained in 81% isolated yield as shown in Scheme 3. That is to say, here we present a practical and scalable synthetic entry to the highly functionalized IPY derivatives.

Scheme 3. Scalability of the Reaction to the Multigram Scale



Control experiments were carried out in order to have a better understanding of this transformation. Intermediate **A** was isolated from the reaction mixture of **1a** and **2a** under the standard reaction conditions by stopping the reaction after a short time (0.5 h) [Scheme 4, eq 1]. Furthermore, we proved

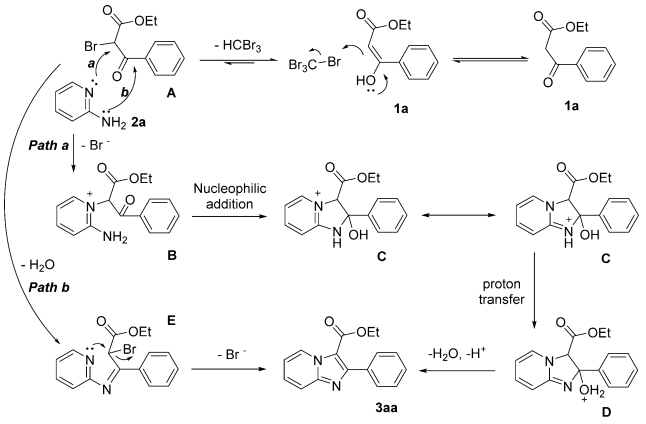
Scheme 4. Control Experiments



that the reaction of intermediate **A** and **1a** gave the same product **3aa** in high yield even without CBr_4 as the promoter [eq 2].[15] These results indicate that **A** is the intermediate of this CBr_4 induced transformation. Tetramethylpiperidin-1-oxyl (TEMPO) and 2,6-di-*tert*-butyl-4-methylphenol (BHT) were employed in the standard reaction as a radical scavenger, and no obvious inhibition was observed [eqs 3 and 4]. These results suggested that no radical process was involved in the present CBr_4 induced reaction.

According to these results, we were able to propose the tentative mechanism of the reactions, as shown in Scheme 5. Taking the reaction of 2-aminopyridine **1a** and ethyl 2-benzoylacetate **2a** for example, in the synthesis of IPY **3aa**, **1a** is first brominated with CBr_4 to give intermediate **A**. The nucleophilic substitution of 2-aminopyridine (**2a**) with intermediate **A** affords intermediate **B**. Subsequent intramolecular nucleophilic addition of **B** provides intermediate **C**. Finally, the proton transfer and the subsequent dehydration and dehydrogenation produced IPY **3aa**. Alternatively (path b), condensation of **A** with **2a** affords imine intermediate **E**. Intramolecular nucleophilic substitution of **E** also provides **3aa**.

Scheme 5. Proposed Mechanism



In summary, we have developed an efficient CBr_4-mediated oxidative C−N bond formation reaction of 2-aminopyridines or 2-aminopyrimidines with β-keto esters or 1,3-diones to construct complex imidazo[1,2-α]pyridines and imidazo[1,2-α]pyrimidines. The starting materials and the promoter are commercially available. The reactions were performed under simple and mild reaction conditions. Further studies on the mechanistic details and synthetic applications of this method are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00137.

Experimental details, compound characterization, and NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: huocongde1978@hotmail.com.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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(13) The X-ray crystal data (excluding structure factors) of compound **3ig** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 1445506. A copy of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: t44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).
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