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Green Method for the Synthesis of Chromeno[2,3-*c*]pyrazol-4(1*H*)-ones through Ionic Liquid Promoted Directed Annulation of 5-(Aryloxy)-1*H*-pyrazole-4-carbaldehydes in Aqueous Media

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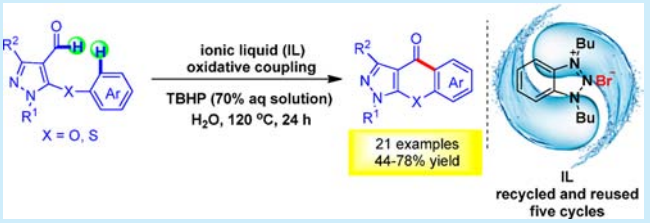
Supporting Information

ABSTRACT: The first classical heterocyclic ionic liquid (IL) promoted C−H bond oxidant cross-coupling reaction for the intramolecular annulation of 5-(aryloxy)-1*H*-pyrazole-4-carbaldehydes to chromeno[2,3-*c*]pyrazol-4(1*H*)-ones has been disclosed. The promoter 1,3-dibutyl-1*H*-benzo[*d*][1,2,3]-triazol-3-ium bromide can be easily recycled and reused with the same efficacies for at least five cycles in aqueous medium. The strategy works smoothly and provides an applicable protocol to construct a wide range of products.



Chromones display a wide range of biological and pharmaceutical activities defined by the substitution pattern of the scaffold.[1] The chromone structures containing a pyrazole ring are significant compounds since pyrazoles are a prominent structural motif that has a rich chemistry with numerous applications,[2] such as in the A_2-subtype selective adenosine receptor antagonist **A**[3] (Figure 1). Thus, construction of the chromone with pyrazole skeleton has always been synthetically attractive.

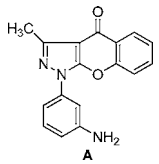


Figure 1. A_2-subtype selective adenosine receptor antagonist.

Recently, oxidative cross-coupling involving a C−H functionalization process has been widely accepted because it is an environmental, sustainable, and higher atom-economic benign method that avoids the use of halides and organometallic reagents.[4] One typical example is cross-dehydrogenative coupling[4a] (CDC) between the aldehyde C−H bond and other C−H bonds, which has offered a powerful tool to produce ketones.[5] In recent years, direct functionalization of the aldehyde C−H bond has been developed under metal-free conditions, wherein direct esterifications,[6] amidations,[7] and ketones[8] in organic solvents were the major subjects.

In recent times, ionic liquids have attracted considerable interest in the context of green synthesis,[9] and the employment of ILs in heterocyclic synthesis from cyclocondensation reactions has been reported.[10] Today, as a supplement to traditional catalysts, the use of ILs which mollify the criteria of economic and effective processes and follow the rules of green and sustainable chemistry is being examined.[11]

Some approaches to chromeno[2,3-*c*]pyrazol-4(1*H*)-ones have been developed. For instance, in 2010, Holzer's group presented the synthesis of fluoro-substituted chromeno[2,3-*c*]pyrazol-4(1*H*)-ones[12a] (Scheme 1, a), and earlier, Cecchi's group reported another way to obtain these compounds using an excess of $POCl_3$ under heating conditions[12b] (Scheme 1, b). Kvitko and co-workers developed pyrazolecarboxylic acid to form these products[12c] (Scheme 1, c). But these methods often suffer from harsh reaction conditions, limited substrate scope, poor substituent tolerance, and low yields. Therefore, the development of effective and much more environmentally benign methods for these compounds is desirable. And as far as we know, there are no examples on the study of the C−H bond activation reaction using classical ionic liquids which contained a heterocyclic structure as promoters. Herein, we report a concise and mild route for the synthesis of chromeno[2,3-*c*]pyrazol-4(1*H*)-ones by using ILs (Figure 2) as the promoter, water as the solvent, and TBHP (70% aqueous solution) as the oxidant without any metal additives or catalysts, which proceeds through the intramolecular oxidative coupling of the aldehyde C−H bonds and aromatic C−H bonds in 5-aryloxy-1*H*-pyrazole-4-carbaldehydes (Scheme 1).

Our investigation began with the reaction of 3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde with TBHP (70% aqueous solution) in H_2O at 120 °C (Table 1). Since the reaction proceeded in a heterogeneous way, while nitrogen-containing ionic liquids can be seen as phase-transfer catalysts, different

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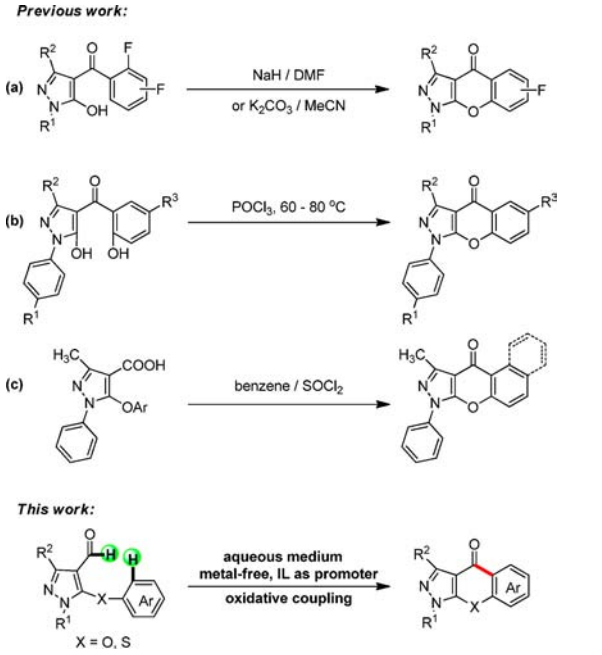
Scheme 1. Traditional and IL-Promoted Methods to Construct Chromeno[2,3-*c*]pyrazol-4(1*H*)-one Structures



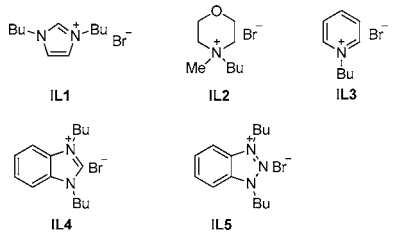
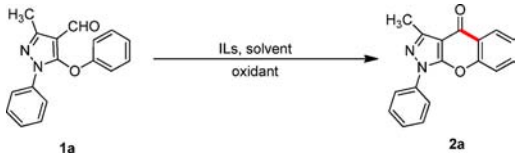


Figure 2. ILs examined in this work.

kinds of ionic liquids (including bromine ions) were added to the reaction system, and indeed, **IL5** 1,3-dibutyl-1*H*-benzo[*d*]-[1,2,3]triazol-3-ium bromide ([Dbbta]Br) exhibited a more positive influence on this oxidative coupling reaction (entries 1−5). Then TBAB was used as a promoter, but this condition led to the product with only 47% yield (entry 6). When CTAB was employed as the promoter, the yield could be enhanced to 63% (entry 7). Next, various solvents were tested, including acetonitrile, dichloromethane, and toluene, while water was the optimal choice (entries 5, 8−10). As to the oxidant, TBHP provided the best yield (entries 5, 11−16). Reducing the amount of **IL5** led to a relatively lower yield (entry 17). However, enhancing the amount of **IL5** did not increase the yield either (entry 18). Lowering the reaction temperature led to a relatively lower yield (entry 19). Interestingly, a shorter reaction time received comparable yield (entries 20 and 21). In an oxidant-free or promoter-free system, compound **2a** was not produced (entries 22 and 23). Consequently, the reaction was carried out with 0.5 equiv of **IL5** as the promoter and TBHP (0.2 mL, 70% aqueous solution) as the oxidant in H_2O (0.1 mL) at 120 °C for 24 h.

With the optimized conditions in hand, the scope of the reaction was investigated. The results are listed in Scheme 2. To our delight, the reaction can serve as a general protocol to the synthesis of various substituted chromeno[2,3-*c*]pyrazol-4(1*H*)-ones. Substrates bearing either electron-withdrawing groups or electron-donating groups all led to the annulation products in

Table 1. IL-Promoted Chromeno[2,3-*c*]pyrazol-4(1*H*)-one Formation under Metal-Free Conditions: Optimization of Reaction Conditions[a]



entry	promoter (equiv)	oxidant	solvent	yield[b] (%)
1	**IL1**	TBHP	H_2O	40
2	**IL2**	TBHP	H_2O	59
3	**IL3**	TBHP	H_2O	36
4	**IL4**	TBHP	H_2O	68
5	**IL5**	TBHP	H_2O	72
6	**TBAB**	TBHP	H_2O	47
7	**CTAB**	TBHP	H_2O	63
8	**IL5**	TBHP	CH_3CN	58
9	**IL5**	TBHP	CH_2Cl_2	42
10	**IL5**	TBHP	toluene	51
11	**IL5**	H_2O_2	H_2O	NR
12	**IL5**	DTBP	H_2O	43
13	**IL5**	$PhI(OAc)_2$	H_2O	45
14	**IL5**	*m*-CPBA	H_2O	NR
15	**IL5**	oxone	H_2O	NR
16	**IL5**	BPO	H_2O	NR
17[c]	**IL5**	TBHP	H_2O	48
18[d]	**IL5**	TBHP	H_2O	58
19[e]	**IL5**	TBHP	H_2O	46
20[f]	**IL5**	**TBHP**	**H_2O**	**73**
21[g]	**IL5**	TBHP	H_2O	61
22[h]		TBHP	H_2O	NR
23[i]	**IL5**		H_2O	NR

[a]Reaction conditions: 1a (0.20 mmol), promoter (0.5 equiv), solvent (0.10 mL), and oxidant (0.2 mL), 120 °C, 36 h. [b]Isolated yield. [c]**IL5** (0.20 equiv). [d]**IL5** (0.75 equiv). [e]Reaction temperature: 100 °C. [f]Reaction time: 24 h. [g]Reaction time: 12 h. [h]**IL5** free. [i]Oxidant free. TBHP = *tert*-butyl hydroperoxide (70% aqueous solution), TBAB = tetrabutylammonium bromide, CTAB = cetyltrimethylammonium bromide, DTBP = di-*tert*-butyl peroxide, *m*-CPBA = *m*-chloroperbenzoic acid, Oxone = potassium monopersulfate, BPO = benzoyl peroxide.

good yields (entries **2b**−**u**). Generally, the aryloxy parts with electron-withdrawing groups were relatively more reactive than those with electron-donating ones and, hence, gave relatively higher yields. Interestingly, substituents at the ortho position of the aryloxy group had little influence on the yield (entries **2g**, **2i**). When the substituent was at the meta position, the products were obtained as isomers in some cases. For example, when the substrate with *m*-OCH_3 was used, the 1:3 mixture products were obtained, and the 7-methoxy-3-methyl-1-phenylchromeno[2,3-*c*]pyrazol-4(1*H*)-one was the major product (entry **2m**). Moreover, when aryloxy parts had two or three substituents, the products were also generated in good yield (entries **2n**−**p**). To further expand the substrate scope, the pyrazole ring unit bearing a 1,3-dimethyl or 1,3-diphenyl group was examined, and it also underwent the standard reaction conditions smoothly to afford the desired product (entries **2r**−**t**). In addition, this strategy could facilitate the synthesis of thiochromeno-4-ones, such as 3,6-dimethyl-1-(phenythio)-chromeno[2,3-*c*]pyrazol-4(1*H*)-one (entry **2u**).

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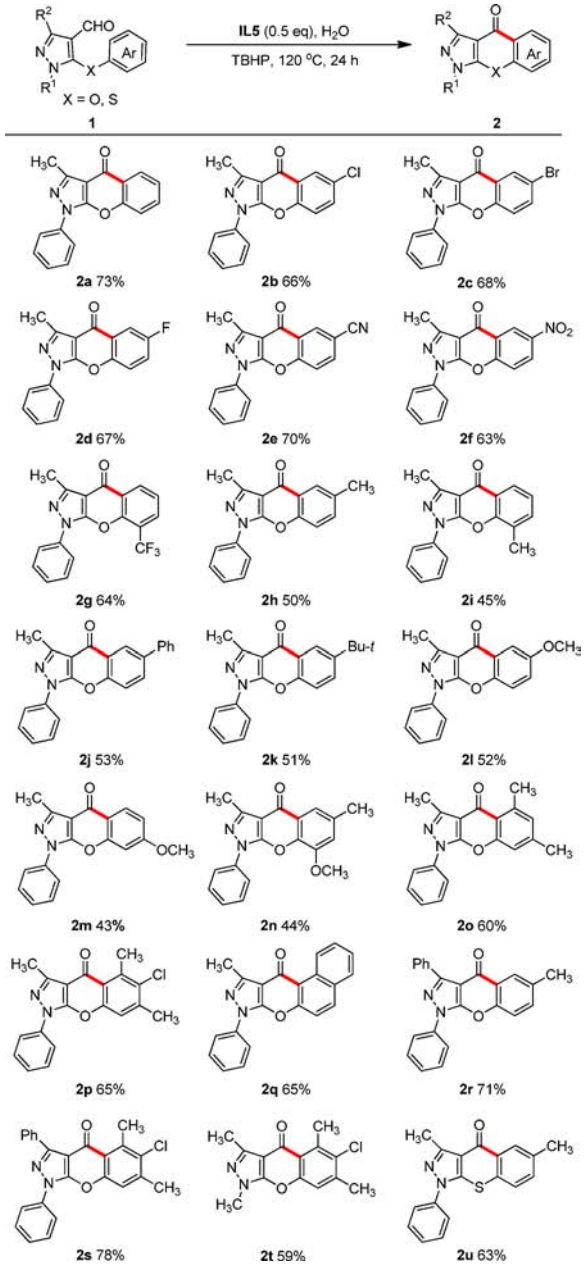
Scheme 2. Scope of the CDC Reaction of 5-(Aryloxy)-1*H*-pyrazole-4-carbaldehydes to Chromeno[2,3-*c*]pyrazol-4(1*H*)-ones[a]

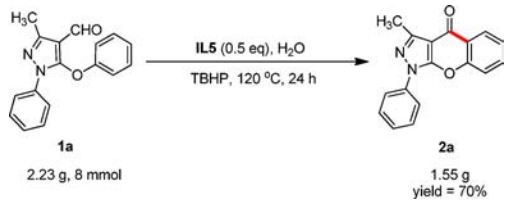


[a]Reaction conditions: 1 (0.20 mmol), **IL5** (0.5 equiv), H_2O (0.10 mL), and TBHP (0.2 mL), 120 °C, 24 h.

To further explore the practicability of our methodology, the IL-promoted reaction was scaled up to the gram scale. A gram-scale oxidative coupling reaction was easily performed under the standard reaction conditions to furnish the desired product in 70% isolated yield, while the model reaction obtained product in 73% isolated yield (Scheme 3).

It is important to note that the ionic liquid **IL5** could be easily recycled. After the reaction was complete, water and ethyl acetate were added, and then the **IL5** was separated in the water layer and reused after drying in vacuo. The **IL5** was utilized repeatedly five times without any loss of activity (Figure 3).

Scheme 3. Gram-Scale Oxidative Coupling Reaction



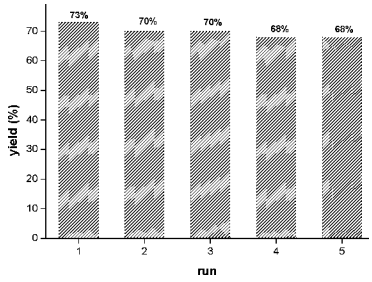
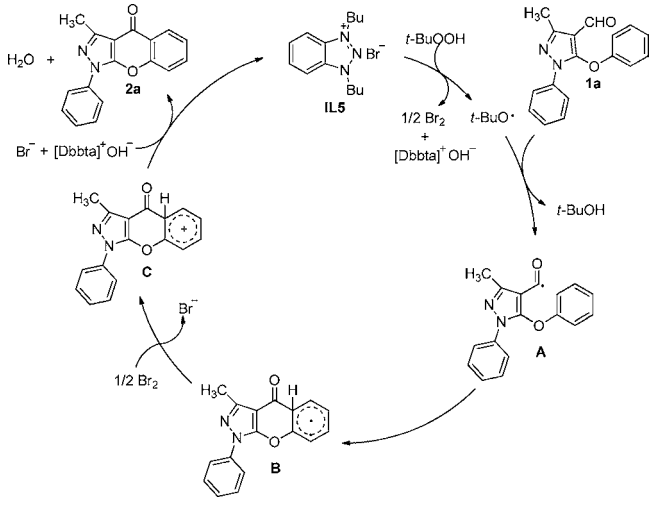


Figure 3. Recycling of **IL5** in the synthesis of 3-methyl-1-phenylchromeno[2,3-*c*]pyrazol-4(1*H*)-one.

In order to elucidate the reaction mechanism, controlled experiments were carried out. TEMPO (2,2,6,6-tetramethylpiperidin-*N*-oxyl) was added to the reaction mixture as a radical scavenger. Compound **2a** was not detected. The acyl radical intermediate was trapped, and the oxyamination product was isolated in 70% yield. Thus, this reaction may be a radical reaction.

According to the above result, a possible mechanism is proposed (Scheme 4). Initially, with the promotion of **IL5**, *tert*-

Scheme 4. Plausible Reaction Mechanism



butoxyl radicals are generated, and then they abstract H• from aldehyde to form acyl radical **A**, which can be well-suited to add to the aryloxy unit to get radical **B**. The ensuing radical **B** will form intermediate **C** via a single-electron-transfer process. Finally, the previously formed hydroxyl anion will act as the proton abstractor from **C**, providing the desired annulation product **2a**.[13a] Another possible process is that the acidic product in B is trapped by the hydroxyl anion to give the radical anion intermediate. Formal liberation of an electron from this intermediate eventually obtains product **2a**.[13b]

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In summary, we have found an IL-promoter directed annulation of 5-aryloxy-1*H*-pyrazole-4-carbaldehydes that serves as a straightforward approach for chromeno[2,3-*c*]pyrazol-4(1*H*)-ones formation via oxidative coupling of aldehyde C−H bond and aromatic C−H bonds under metal-free conditions in aqueous medium. In addition, the reaction can tolerate diverse functional groups and can be applied to obtain a rather wide range of products. Furthermore, promoter **IL5** can be easily recycled and reused with the same efficacies for five cycles. In this sense, it is a useful complementary method for synthesizing chromeno[2,3-*c*]pyrazol-4(1*H*)-ones.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedure, NMR spectra, and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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