A Novel One-pot Synthesis of Pyrroloquinoline and Pyrroloisoquinoline Derivatives in Ionic Liquid

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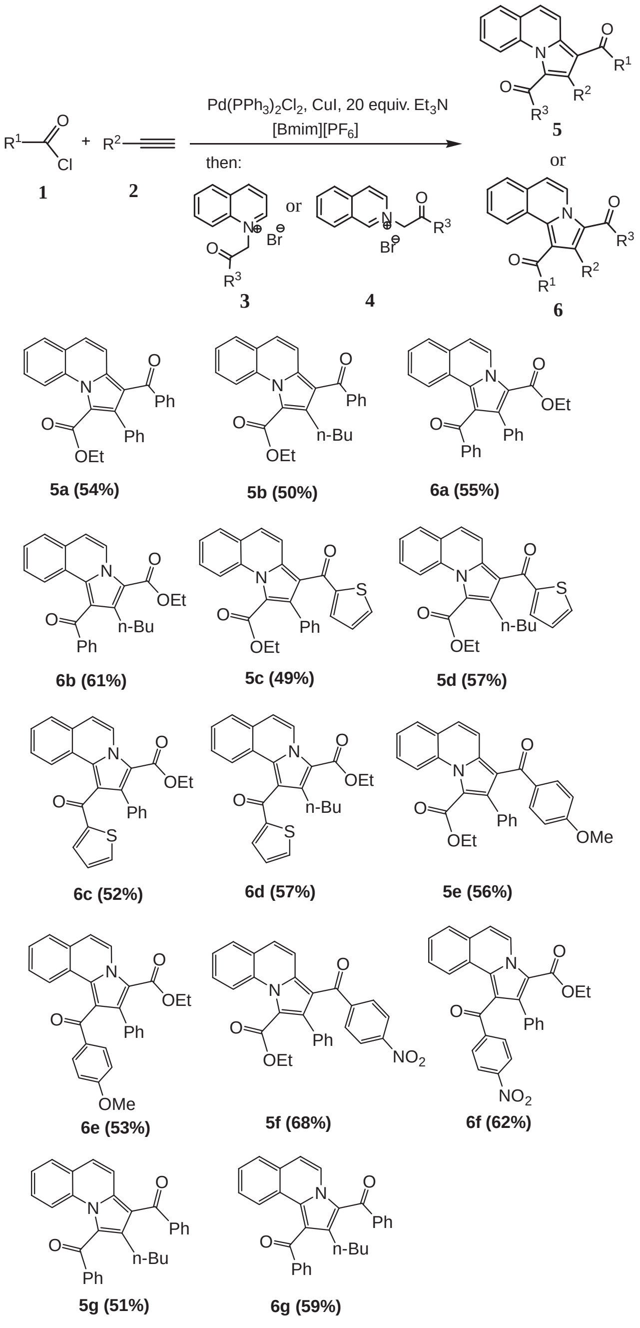
A Sonogashira coupling–1,3-dipolar cycloaddition sequence of a (hetero)arenecarbonyl chloride **1**, a terminal alkyne **2**, and a suitable quinolinium bromide **3** or isoquinolinium bromide **4** was carried out in ionic liquid on the basis of a consecutive one-pot three-component process. Optimization of ionic liquid and recycling of the catalyst were discussed.

Multicomponent and sequential one-pot processes address very fundamental principles of synthetic efficiency and reaction design,[1] and they are steadily gaining considerable and increasing academic, economic, and ecological interests. Additionally, the aspect of the modular chemistry of one-pot reactions can be readily expanded into combinatorial and solid-phase syntheses[2] promising manifold opportunities for developing novel leading structures of pharmaceuticals, catalysts, and even novel molecule-based materials.

In recent years, room-temperature ionic liquids are being considered as the potent alternative to volatile organic solvents for numerous catalytic reactions.[3] Facile immobilization of the metal-catalyst, easy work-up, and quick separation procedures associated with the ionic liquids make them potential candidates as reaction media for a wide range of inorganic and organic reactions.[4] The Sonogashira coupling reaction is frequently utilized as a key step in natural product synthesis.[5] Recent applications of this reaction include the synthesis of oligomeric, polymeric, and dendritic acetylene compounds, which are potentially useful in optical and electronic applications.[6] The Sonogashira coupling reaction is typically carried out in organic solvents, such as toluene, THF, and DMF, and a stoichiometric amount of base is required to trap the HX produced in the reaction. If the Sonogashira coupling could be carried out in ionic liquids,[7] the reaction would have a great advantage in terms of catalyst recycling, since the organic products could be readily separated from the transition-metal catalysts dissolved in the ionic liquids by simple extraction with a conventional organic solvent.[8]

As a part of our program directed to design novel multicomponent reactions based on in situ activation of alkynes by the Sonogashira coupling, we became interested in sequentially combining cycloadditions with cross-coupling reactions. The alkynone products of the Sonogashira alkynylation of electron deficient heterocyclic halides or acid chlorides are highly reactive bifunctional electrophiles that open entries to multi-component synthesis of biologically relevant heterocycles such as pyrazoles, tetrahydro-β-carbolines and pyrimidines. Here, we describe utilization of ionic liquid as a reaction medium for the three-component one-pot synthesis of pyrroloquinoline and pyrroloisoquinoline derivatives based upon a consecutive Sonogashira coupling–1,3-dipolar cycloaddition sequence.

A (hetero)arenecarbonyl chloride **1** and a terminal alkyne **2** were treated under the reaction conditions of Pd/Cu-catalyzed Sonogashira coupling in an ionic liquid[9] at room temperature



Scheme 1.

Table 1. Effects of different ionic liquids on the Sonogashira coupling–cycloaddition

No.	Ionic liquid	Yield/%
1	[BMIm]PF_6	57
2	[BMIm]BF_4	53
3	[EMIm]BF_4	42
4	[BMIm]NTf_2	39
5	[BMPy]BF_4	12

and after 3 h, a quinolinium bromide **3** or isoquinolinium bromide **4** was added to furnish, after 12 h of stirring at 70 °C, an pyrroloquinoline **5** or pyrroloisoquinoline **6** (Scheme 1). All coupling products were easily separated from the catalyst and solvent by extraction with ethyl acetate in hexane or ether. The coupling reaction proceeded smoothly, irrespective of whether the substituents of the arenecarbonyl chlorides were electron-donating or electron-withdrawing, to give the corresponding products in 49–68% yields.

We searched for the most suitable ionic liquid for the Sonogashira coupling–cycloaddition reaction by the use of the 1-butyl-3-methylimidazolium hexafluorophosphate ([BMIm]-PF_6), 1-butyl-3-methylimidazolium tetrafluoroborate ([BMIm]-BF_4), 1-ethyl-3-methylimidazolium tetrafluoroborate ([EMIm]-BF_4), 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide ([BMIm]NTf_2), and 1-butyl-1-methylpyrrolidinium tetrafluoroborate ([BMPy]BF_4) as a reaction medium. We carried out the three-component one-pot reaction employing 2-thiophenecarbonyl chloride, 1-hexyne and 1-(2-ethoxy-2-oxoethyl)quinolinium bromide as substrates, and used $PdCl_2(PPh_3)_2$ and CuI as the cocatalyst which readily dissolves in ionic liquid (Table 1). Some ionic liquids such as [BMIm]PF_6 and [BMIm]BF_4 showed good solvent efficiency as a reaction medium (Entries 1 and 2 in Table 1). Some other ionic liquids, such as [EMIm]BF_4 and [BMIm]NTf_2, also worked well, but the yields of **5d** were slightly inferior (Entries 3 and 4 in Table 1). However, [BMPy]BF_4 showed lower efficiency towards the synthesis of **5d** (Entry 5 in Table 1). Thus, among the five ionic liquids tested, a superior performance of [BMIm]PF_6 could be easily recognized.

After determining of the most suitable ionic liquid, we also carried out catalyst recycling studies. We still used 2-thiophenecarbonyl chloride, 1-hexyne, and 1-(2-ethoxy-2-oxoethyl)quinolinium bromide as substrates for a model reaction, and [BMIm]PF_6 was used as a reaction medium. After completion of reaction, the reaction mixture was extracted with ethyl acetate in hexane or ether to separate the products from the catalyst. The resulting ionic liquid containing the Pd/Cu cocatalyst could be reused successfully several times with only a slight loss in its activity (Table 2).

Table 2. Recycling studies of catalyst in ionic liquid

Number of cycles	Yield/%
1	57
2	52
3	49
4	48
5	45

Using $PdCl_2$–$(PPh_3)_2$ and CuI as cocatalyst and diisopropylamine or piperidine as base in place of triethylamine, the Sonogashira coupling–cycloaddition reaction also proceeded smoothly and showed comparable efficiency towards the synthesis of **5d**. For comparison, we also tested a similar reaction with $PdCl_2$–$(PPh_3)_2$ and CuI in organic solvents, but the results were less satisfactory (yield of **5d**: toluene (16%), THF (27%), and CH_3CN (23%).

In conclusion, the consecutive one-pot three-component coupling–1,3-dipolar cycloaddition sequence of a (hetero)arenecarbonyl chloride, a terminal alkyne, and a suitable quinolinium or isoquinolinium salt in ionic liquid is a novel methodological showcase for the combination of a cross-coupling and a sequential cycloaddition, giving rise to a variety of pyrroloquinoline or pyrroloisoquinoline derivatives. The use of an ionic liquid permitted the product to be easily separated from the catalyst. The recovered catalyst could then be reused. Further studies are directed to the methodological development of this novel three-component reaction and are currently under progress.

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