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Lithiation and functionalization of 1-alkynylimidazoles at the 2-position

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ABSTRACT

Functionalization reactions of 1-alkynylimidazoles involving the formation of their 2-lithio derivatives followed by addition of various electrophiles are presented. This allows access to previously unreported 1,2-dialkynylimidazoles via 1-alkynyl-2-iodoimidazoles. The use of an aldehyde or sulfonimine electrophiles allows the direct formation of bicyclic ring systems.

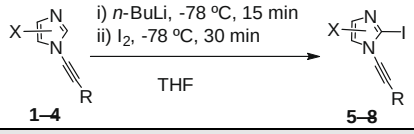
1. Introduction

Imidazoles and benzimidazoles are molecules of wide interest and importance due to their utilization as key scaffolds in nature[1–4] and pharmaceutical products.[5–7] We recently reported a coupling reaction between imidazoles and bromoalkynes mediated by copper complexes.[8] This methodology allows efficient access to 1-alkynylimidazoles. The rapid elaboration of polycyclic heterocycles from a variety of N-substituted alkynes has been reported recently.[9–13] Application of these strategies, or alternative strategies involving the thermal cyclization of 1,2-dialkynylimidazoles,[14] requires functionalization of the readily available 1-alkynylimidazoles at the 2-position. Functionalization of 1-protected imidazoles at the 2-position has been reported many times in the literature. One methodology is based on the quaternarization of the pyridine-like nitrogen (typically with Boc_2O), allowing the formation of an intermediate ylide which can be trapped by different electrophiles.[15] An alternative and widely used methodology consists of the generation of the lithiated intermediate[16] at the 2-position by the action of a strong base (typically *n*-BuLi) followed by addition of an electrophile reagent.[17] Using this process, observed yields vary significantly with reaction conditions and the nature of protected group on the pyrrole-like nitrogen. The main issues in applying this strategy on 1-alkynylimidazoles concern the unknown stability of the ynamine moiety under strong basic conditions and potential instability of the resulting lithiated intermediate. We are aware of only one previous report of deprotonation/lithiation of a heterocycle adjacent to an *N*-alkynyl substituent.[18] The work described here reports the successful application of this strategy in the functionalization of 1-alkynylimidazoles to 2-substituted-1-alkynylimidazoles.

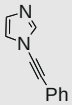
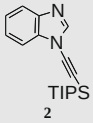
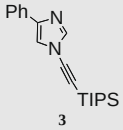
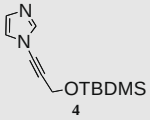
2. Result and discussion

The deprotonation of 1-alkynylimidazole **1** (Table 1) was studied by deuterolysis experiment. Addition of *n*-BuLi (2.5 M in hex-

Table 1
Iodination of 1-alkynylimidazoles



1–4 **5–8**

Entry	Starting material	*n*-BuLi equiv	I_2 equiv	Product, yield
1	 **1**	1.2	0.9	**5**, 50%
2	**1**	1.0	1.0	**5**, 87%
3	**1**	1.2	1.2	**5**, 74%
4	 **2**	1.0	1.0	**6**, 77%
5	 **3**	1.0	1.0	**7**, 61%
6	 **4**	1.0	1.0	**8**, 82%

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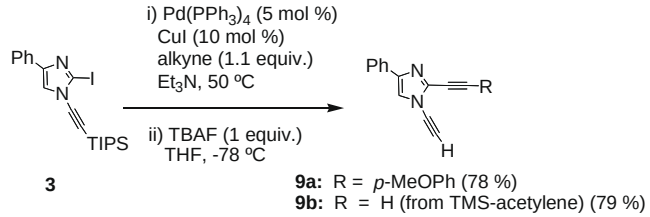
ane) to 1-(2-phenylethynyl)-imidazole (**1**) in THF at −78 °C was followed by quenching of reaction mixture aliquots with D_2O at different time periods (15, 30, and 60 min). ^{1}H NMR spectra of the quenched reaction products showed an almost complete disappearance of the signal for the proton at the 2-position on the imidazole ring after 15 min at −78 °C (95% deuterium incorporation). The ^{1}H NMR spectra obtained after 30 min and 1 h at −78 °C were similar to the those of the 15 min sample, indicating that the 2-lithiated intermediate is stable under these conditions; however, after warming the reaction mixture, we noticed the formation of an oligomeric product at approximately −40 °C.

Initial attempts to access 2-substituted-1-alkynylimidazoles focused on trapping the 2-lithio species with iodine. After deprotonation of **1** with *n*-BuLi at −78 °C for 15 min, solid iodine was added at −78 °C and the reaction mixture was stirred for an additional 30 min at −78 °C. Gratifyingly, this led to the isolation of the 2-iodo-1-(phenylethynyl)imidazole (**5**) in moderate yield (Table 1, entry 1). Optimization of the equivalents of base and iodine indicated that the use of excess reagent is detrimental to reaction yield (Table 1, entries 1 and 3). We are assuming that the excess of base or iodine may react with the carbon–carbon triple bond. When exactly one equivalent of each reagent was used, the yield of **5** increased from 50% to 87% (Table 1, entry 2).

Under the optimized conditions, three different substrates afforded iodinated products in moderate to good yields (Table 1, entries 4–6). The methodology showed good tolerance toward variations in the imidazole ring system (benzimidazole and 4-phenylimidazole, Table 1, entries 4 and 5) and carbon–carbon triple bond substitution (Ph, TIPS, and CH_2OTBDMS, Table 1, entries 3, 4, and 6). Thus, despite some limitations due to the stability of the 2-lithio derivative and the reactivity of the triple bond, the ynamine moiety of 1-alkynylimidazoles acts as an efficient blocking group of the pyrrole-like nitrogen, enabling iodination at the 2-position.

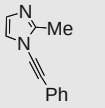
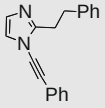
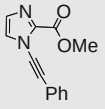
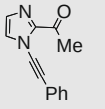
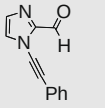
To demonstrate the utility of this new strategy, the compound **3** was engaged in coupling reaction with 4-methoxyphenylacetylene and trimethylsilylacetylene (Scheme 1). In both cases, the 4-substituted-1,2-dialkynylimidazoles **9a** and **9b**, respectively, were obtained in good yields after Sonogashira coupling and silyl deprotection. This strategy represents a significant advance since 4-substituted-1,2-dialkynylimidazoles cannot be produced using our previous strategy.[19]

We have investigated the use of electrophiles other than iodine to intercept the 2-lithio derivative of 1-phenylethynylimidazole (Table 2). Iodomethane gave the expected methylated compound **10** in almost quantitative yield (Table 2, entry 1). When phenylethylbromide, -iodide,[20] -tosylate,[21] and -triflate[22] were examined as electrophiles, the triflate derivative was the only one to afford the 2-alkylated product **11** (60% yield, Table 2, entry 2). The lack of reactivity of 1-dimethylaminomethyl-protected imidazole anion with phenylethyliodide and -tosylate has been previously reported.[23] Moreover, the 2-lithio species derived from 1-alkynylimidazoles may be also limited by ring fragmentation as is observed for 2-lithiated oxazole species.[24] In the literature, the limited reactivity of the 2-lithio imidazole species toward these



Scheme 1. Synthesis of new 4-substituted-1,2-dialkynylimidazoles.

Table 2
Reaction of 1-alkynylimidazoles with different electrophiles

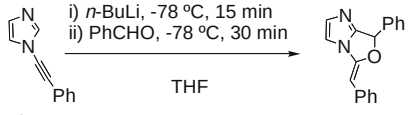
Entry	Electrophile	Product	Yield
1	MeI		**10**, 96%
2	$Ph(CH_2)_2OTf$		**11**, 60%
3	$ClCO_2Me$		**12**, 61%
4	EtOAc		**13**, 60%
5[a]	$(CH_3)_2NCHO$		**14**, 65%

[a] The reaction was quenched with 5 mL of 1 M HCl solution.

electrophiles has led to alternative routes to the 2-(2-arylethyl) derivatives involving either deprotonation of a 2-methyl derivative and alkylation of the resulting 2-lithiomethyl species[23] or a Wittig-based strategy where an (arylmethyl)triphenylphosphonium salt and 2-formylimidazole were coupled followed by reduction.[25] In our case, **11** can be prepared directly by employing the corresponding triflate electrophile. The successful synthesis of 2-alkyl-1-alkynylimidazoles constitutes the starting point for structure–activity relationship studies. Although a number of biologically active 1-alkyl-2-alkynylimidazoles are known,[26] the regioisomeric 2-alkyl-1-alkynylimidazoles such as compounds **10** and **11** are new. These can be used as model compounds to evaluate the biological relevance of the regiochemistry of the carbon–carbon triple bond of the previously reported alkynylimidazoles.

Other electrophiles can also be used to trap the 2-lithio species. Methylchloroformate, ethyl acetate, and dimethylformamide can all be employed to afford ester **12**, ketone **13**, and aldehyde **14** in 60%, 61%, and 65% yield, respectively (Table 2, entries 3–5).

Finally, when benzaldehyde was employed, a different type of product was formed in 50% yield. The ^{13}C NMR of this product showed the disappearance of the carbon–carbon triple bond signals and the ^{1}H NMR spectrum showed a signal at 6.5 ppm attributed to an olefinic proton. Although these observations are consistent with a product in which the intermediate alcoholate adds to the ynamine moiety, the structure could not be unambig-



Scheme 2. Direct route to dihydroimidazo[1,2-*c*]oxazole.

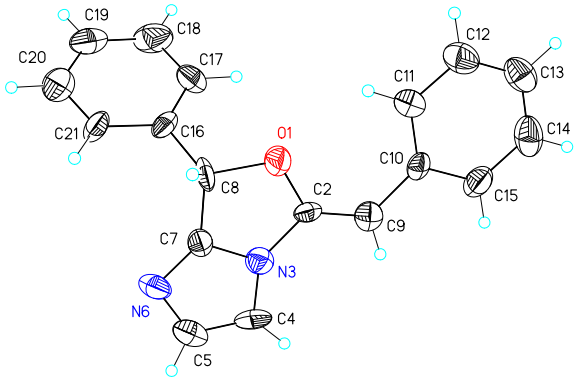


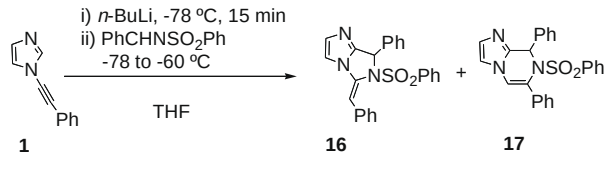
Figure 1. Structure of **15** determined by X-ray crystallography. One of two non-centrosymmetric molecules of **15** from the unit cell is shown. Displacement ellipsoids are scaled to the 50% probability level.

uously assigned based on spectral data. Fortunately, the product was crystalline and the structure solved by X-ray crystallography was assigned as the 5,7-dihydroimidazo[1,2-*c*]oxazole **15** (Scheme 2, Fig. 1).

5,7-Dihydroimidazo[1,2-*c*]oxazoles have been reported a few times in the literature for their biological properties and are generally prepared by a condensation reaction between 2-hydroxymethylimidazoles and aldehydes.[27] The formation of **15** can be classified as a 5-*exo*-dig ring closure reaction of the intermediate alcoholate onto the imidazole 1-alkynyl substituent.

The 2-lithio-1-phenylethynyl-1*H*-imidazole was also allowed to react with *N*-benzylidenebenzenesulfonamide[28] at −78 °C. The solution was allowed to warm to −60 °C after the addition of the sulfonimine and the reaction was quenched by the addition of water (Scheme 3).

Two products were formed, one of these products, obtained in 24% yield, was assigned the 5-benzylidine-6,7-dihydromidazo[1,5-*a*]imidazole structure **16** based on comparison of its NMR spectral properties with that of **15**. The 7,8-dihydroimidazo[1,2-*a*]pyrazine structure of **17**, obtained in 23% yield, was determined by X-ray crystallography (Fig. 2).



Scheme 3. Direct route to 5-benzylidine-6,7-dihydromidazo[1,5-*a*]imidazole **16** and 7,8-dihydroimidazo[1,2-*a*]pyrazine **17**.

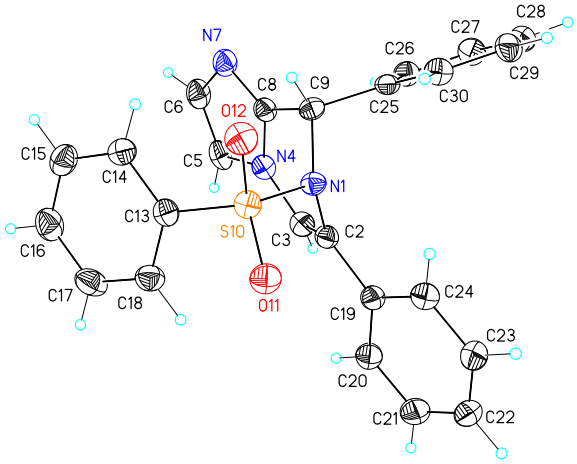


Figure 2. Structure of **17** determined by X-ray crystallography. Displacement ellipsoids are scaled to the 50% probability level.

Interestingly, in this case, the presumed intermediate sulfonamide anion undergoes both 5-*exo*-dig and 6-*endo*-dig cyclization with no apparent selectivity for one mode versus the other.

3. Conclusion

The synthesis of 1-alkynylimidazoles with various substituents on the 2-position has been accomplished.[29] The strategy employed allows the presence of different substituents on the carbon–carbon triple bond and the imidazole core. In the case of 2-iodo derivatives, a subsequent Sonogashira coupling was realized to achieve the synthesis of previously inaccessible 1,2-dialkynylimidazoles. The method developed in this Letter also provides a new, concise route to the synthesis of the 5,7-dihydroimidazo[1,2-*c*]oxazole, 5-benzylidine-6,7-dihydromidazo[1,5-*a*]imidazole, and 7,8-dihydroimidazo[1,2-*a*]pyrazine bicyclic ring systems.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.06.133.

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29. *Typical procedure for the synthesis of 2-methyl-1-(2-phenylethynyl)-1H-imidazole* (**9**): To a solution of 1-(2-phenylethynyl)-1*H*-imidazole **1** (84 mg, 0.5 mmol) in THF (5 mL) under argon at −78 °C was added *n*-BuLi (0.200 mL of 2.5 M solution in hexane, 0.5 mmol). The reaction mixture was stirred for 15 min at −78 °C prior to the addition of MeI (0.031 mL, 0.5 mmol). After stirring for 30 min at −78 °C, the mixture was quenched with water (5 mL, method A) or 1 M HCl solution (5 mL, method B) and the temperature was allowed to rise to room temperature. The reaction mixture was then extracted with CH_2Cl_2 (3 × 25 mL), the combined organic layers were dried over Na_2S0_4, and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (0–20% EtOAc/hexane) to afford 88 mg (96%) of **9** as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.46 (2H, m), 7.38–7.33 (3H, m), 7.08 (1H, s), 6.90 (1H, s), 2.53 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.7 (br s), 131.5 (2C), 128.7, 128.4 (2C), 127.7, 121.3, 121.1, 78.0, 72.4, 13.2; IR (neat) 2265, 1547, 1500, 1424, 1285, 1183, 1153, 982 cm^{-1}; MS (CI) 183 (M+1, 100%); HRMS (CI) calcd for $C_{12}H_{11}N_2$ ($M+H^+$) 183.0919, found 183.0917.