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Three-component reaction between imidazoles, isocyanates, and cyanophenylacetylene: a short-cut to *N*-(*Z*)-alkenylimidazole-2-carboxamides

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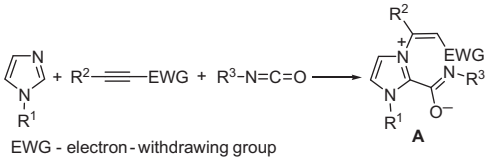
ABSTRACT

1-Substituted imidazoles, isocyanates, and cyanophenylacetylene react under mild (rt), non-catalytic solvent-free conditions to give (*Z*)-(2-cyano-1-phenylethenyl)imidazole-2-carboxamides in up to 72% yields and with ca. 100% stereoselectivity. The reaction starts from the initial formation of zwitterion/carbene intermediates captured by the isocyanate as the electrophile followed by migration of the alkenyl moiety from the N-3 atom to the anionic center at the carboxamide nitrogen. Thus, the reaction provides an easy access to a novel family of functionalized imidazoles.

Functionalized imidazoles are known to be a source of a diversity of biochemically important species such as the essential amino acids, vitamins, alkaloids, drugs, and their precursors including histidine, histamine, allantoin, pilocarpine, etc.[1,2] Imidazole-tailored pharmaceuticals such as cimetidine (an inhibitor of gastric acid secretion), etomidate (an anesthetic), ketoconazole (an antifungal medication),[2–4] eprosartan and losartan (antihypertensives), and metronidazole (a chemotherapeutic)[5] are commonly used in clinics. A number of imidazole derivatives exhibit antithrombic,[6] antiproliferative,[7] antihelminthic, antitumor, fungicidal, and anti-inflammatory[8,9] properties. Among functionalized imidazoles, representatives with carboxamide functionality are less well studied although they deserve much more attention in view of the fact that dacarbazine, a novel antitumor drug, contains the carboxamide function in the imidazole ring.[5] Some imidazole-2-carboxamides were reported to act as human CB1 receptor inverse agonists,[10] that is, as promising anti-obesity and antidiabetes pharmaceuticals. However, they were synthesized via 4 or 5 steps using a high temperature (180–220 °C), benzoin cyclization or condensation, chlorination with phosphorus oxychloride, lithiation with BuLi, and reduction over Pd/C in an overall yield of about 20%.

The reactions of imidazoles with isocyanates allow imidazole carboxamides to be synthesized in a one-pot procedure,[11,12] although unsubstituted imidazoles under mild conditions lead only to imidazole-1-carboxamides, which partially dissociate into their precursors upon melting, or in solution. Imidazoles react with isocyanates upon boiling in nitrobenzene (210 °C) or diphenyl ether (259 °C) to give imidazole-2-carboxamides in 18–92% yields depending on the structures of the starting materials.[13] Later, the carboxamide function was introduced elegantly into position 2 of the imidazole ring via lithiation of 1-(dimethylaminomethyl)imidazole with BuLi followed by the treatment with an isocyanate.[14] This strategy was further developed to synthesize imidazole-2,5-dicarboxamides.[15] 1,3-Dimethylimidazolium-2-carboxylate and 4-carboxylate on decarboxylation generate the corresponding carbenes, imidazol-2-ylidene and imidazol-4-ylidene, which are trapped by isocyanates to give imidazolium-amidates.[16] Another type of imidazolium carbene or its zwitterionic precursors originated from the nucleophilic addition of 1-substituted imidazoles to electron-deficient acetylenes. Interception of these carbenes or the preceding zwitterions by an appropriate electrophile is the key step of a rapidly developing general synthetic strategy for the functionalization of imidazole rings.[17–21] Therefore, the three-component reactions between 1-substituted imidazoles,



Scheme 1. Generation of imidazole carboxamide zwitterions **A**.

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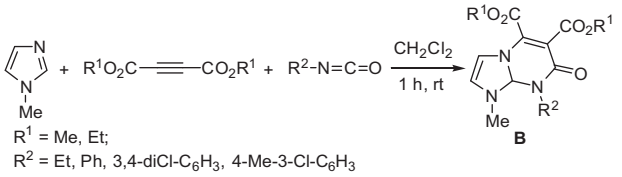
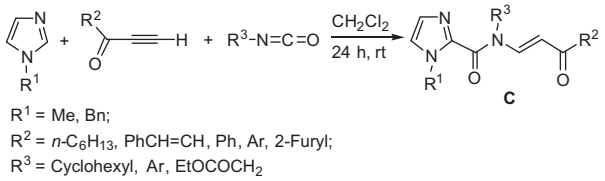


Scheme 2. Synthesis of tetrahydroimidazo[1,2-*a*]pyrimidines **B**.



Scheme 3. Synthesis of imidazole-2-carboxamides **C**.

isocyanates, and electron-deficient acetylenes might be expected to lead to the corresponding zwitterionic forms of the imidazole carboxamides **A**, similar to those described previously[16] (Scheme 1).

Meanwhile, against expectations, the above reaction with acetylenedicarboxylates (rt, CH_2Cl_2, 1 h) was reported to furnish tetrahydroimidazo[1,2-*a*]pyrimidines **B**[22] (Scheme 2).

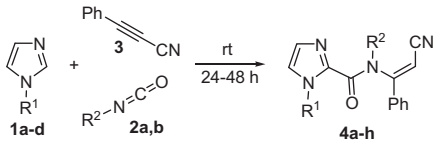
However, when acetylenic ketones were employed as the acetylenic components (rt, CH_2Cl_2, 24 h) in this reaction, imidazole -2-carboxamides **C** were actually obtained, presumably via intermediates of type **A**[23] (Scheme 3).

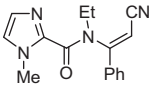
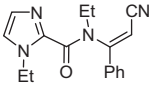
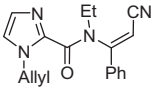
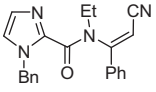
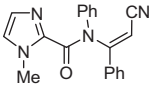
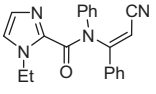
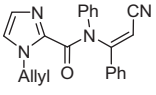
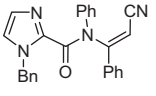
Thus, it became clear that the outcome of this three-component reaction depends strongly on the structure of the starting materials, first of all, on the acetylene and on the reaction conditions.

In the light of these results we have undertaken a study of the three-component reaction between 1-substituted imidazoles **1a**–**d**, isocyanates **2a**,**b**, and cyanophenylacetylene **3** aiming at, (i) the synthesis of a novel family of imidazole-2-carboxamides with an acrylonitrile substituent on the amide nitrogen (Table 1), (ii) the evaluation of the competition between imidazole-2-carboxamide **4a**–**h** formation and C(2)-vinylation with cyanophenylacetylene and, (iii) the simultaneous synthesis of (*Z*)-2-(2-cyano-1-phenylethenyl) imidazoles **5a**–**d**.

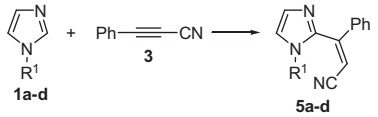
The reaction was carried out at room temperature without a catalyst or solvent for 24–48 h; the reactant-molar ratio was 1:1:1. The order of mixing the reactants was important. First, cyanophenylacetylene was dissolved in the isocyanate and then the

Table 1
Synthesis of (*Z*)-(2-cyano-1-phenylethenyl)imidazole-2-carboxamides **4a**–**h**

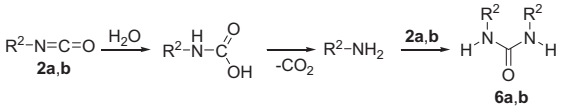


Imidazole		Isocyanate		Time (h)	Imidazole-2-carboxamide		Isolated yield[a] (%)
	**1a**	Et-N=C=O	**2a**	24		**4a**	50
	**1b**	Et-N=C=O	**2a**	48		**4b**	65
	**1c**	Et-N=C=O	**2a**	24		**4c**	28
	**1d**	Et-N=C=O	**2a**	24		**4d**	55[b]
	**1a**	Ph-N=C=O	**2b**	48		**4e**	72
	**1b**	Ph-N=C=O	**2b**	48		**4f**	34
	**1c**	Ph-N=C=O	**2b**	48		**4g**	39
	**1d**	Ph-N=C=O	**2b**	48		**4h**	69[b]

[a] Based on imidazole **1**.
[b] For homogenization, 0.1 mL of MeCN was added to the reaction mixture (1:1:1 mmol).



Scheme 4. Synthesis of (*Z*)-2-(2-cyano-1-phenylethenyl)imidazoles **5a**–**d**.



Scheme 5. Formation of the *N*,*N*′-disubstituted carbamides **6a**,**b**.

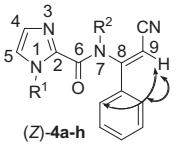


Figure 1. Cross-peaks in the 2D NOESY spectra of imidazole-2-carboxamides **4a**–**h**.

imidazole was added. Mixing of the imidazole with cyanophenylacetylene prior to the addition of an electrophile favored a competitive binary C(2)-vinylation reaction[24,25] (see below). The progress of the reaction was followed by IR spectroscopy until the disappearance of the absorption bands at 2250–2270 cm^{-1} belonging to the isocyanate N=C=O entity and CN bond attached to the acetylene moiety was complete. The products were isolated by column chromatography (neutral Al_2O_3 with chloroform/benzene/ethanol, 20:4:1, as eluent).

The major products were imidazole-2-carboxamides **4a**–**h** isolated in 28–72% yields (Table 1) based on imidazole **1**. In some cases, when starting imidazole was recovered, for example, for carboxamides **4d**, **4e**, **4f**, and **4g**, the yields when calculated on the imidazole reacted were 73%, 98%, 55%, and 65%, respectively.

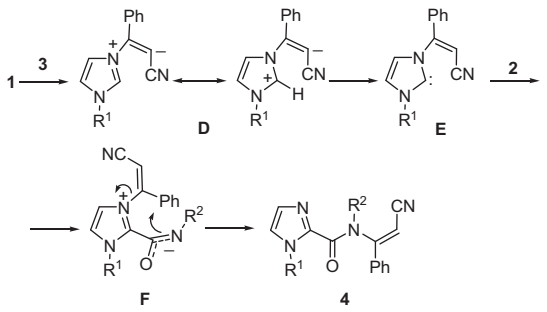
The *Z*-stereoselectivity of the reaction was always close to 100% (in no case was the *E*-isomer detected in the ^1H NMR spectrum of the reaction mixture). This high stereoselectivity, allowing for the first time the introduction of a (*Z*)-2-cyanophenylethenyl moiety into the carboxamide function of 1-substituted imidazoles, represents an obvious advantage of this synthesis. Its other benefit, unlike the procedures relating to similar reactions,[22,23] is the solvent-free, 'green', ecologically benign protocol. As distinct to the recent reports on similar reactions, we have detected a competitive stereoselective vinylation of imidazole position 2 with an electron-deficient acetylene (cyanophenylacetylene) to deliver (*Z*)-2-(2-cyano-1-phenylethenyl)imidazoles **5a**–**d** in trace to 37% yields (Scheme 4). This process was previously observed for the binary reaction between 1-substituted imidazoles and cyanophenylacetylene.[24,25]

In some cases, *N*,*N*′-disubstituted carbamides **6a**,**b** were isolated from the reaction mixture. This definitely had resulted from the commonly known hydrolytic decomposition (due to the adventitious water) of the isocyanates **2a**,**b** to carbon dioxide and amines which then add to a second molecule of the isocyanate (Scheme 5).[26]

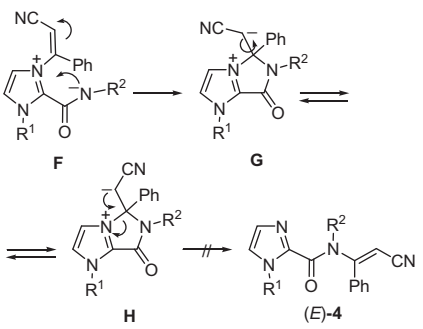
The structures of the imidazole-2-carboxamides **4a**–**h** were unambiguously assigned by ^1H, ^{13}C, 2D NMR, and IR spectroscopy. In their ^1H NMR spectra, the ethenyl protons H-9 appear as singlets in the δ 5.37–5.47 region. In the ^{13}C NMR spectra, the ethenyl carbons C-8 and C-9 resonate at δ 160.8–161.8 and δ 92.9–93.4, respectively, the C-6 carbons were observed at δ 160.3–160.9 and the CN carbons at δ 116.1–116.6. In the NOESY spectra of carboxamides **4a**–**h**, the correlation between the olefinic H-9 and the *ortho*-protons of the phenyl ring was manifested in support of the *Z*-configuration of the 2-cyano-1-phenylethenyl moiety (Fig. 1). In the IR spectra of carboxamides **4a**–**h**, the C≡N and C=O stretching vibrations appeared at 2213–2216 and 1655–1670 cm^{-1}, respectively, the stretching vibration bands of the C=C bond of the ethenyl moiety overlapped with the imidazole and benzene ring C=C stretching at 1601–1607 cm^{-1}.

One of the plausible mechanisms for the formation of imidazole-2-carboxamides is assumed to involve the zwitterionic intermediate **D**, the adduct of the starting imidazole with cyanophenylacetylene, which undergoes proton transfer from position 2 to the carbanionic center to generate the carbene **E**. Due to the unfavorable *trans*-orientation of the carbanionic site relative to the imidazole ring, this process most probably occurs in an intermolecular manner (instead of the intramolecular). The stereochemistry of a zwitterion **D** is the expected result of a concerted nucleophilic addition to the triple bond, which is known to be *trans*-oriented relative to the attacking nucleophile and the proton donor species.[27,28] The intermediate **E** is then likely intercepted by the isocyanate molecule to form zwitterion **F** with the ambident *N*,*O*-anionic moiety. The migration of a cyanophenylethenyl radical from position 3 to the anionic nitrogen atom in the intermediate **F** entails the functionalization of the imidazole ring (Scheme 6). Given the high stereoselectivity of this process, it might be expected to proceed in a consistent fashion, that is., the CN-3 bond cleavage is accompanied by simultaneous formation of the N (of the anionic carboxamide moiety)-C bond. Such a concerted migration explains the *Z*-stereochemistry of the migrating alkenyl group.

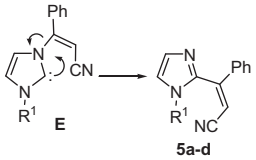
The possible addition/elimination alternative[23] might compromise the stereoselectivity owing to the free rotation along the pseudo-ordinary C–C bond thus temporarily formed (*cf.* intermediate rotamers **G** and **H**), Scheme 7. However, the absence of the (*E*)-**4** isomer in the reaction mixture (^1H NMR) may not provide the ultimate argument against the addition/elimination process provided



Scheme 6. Tentative mechanism of imidazole-2-carboxamide **4a**–**h** formation.



Scheme 7. Alternative mechanism of addition/elimination.



Scheme 8. 3,2-Stereoselective migration of the 1-phenyl-2-cyanoethenyl group.

that the *Z*-isomers of the final products are much more thermodynamically favorable over the *E*-isomers. At the same time, the mutual disposition of CN and phenyl functions in the rotamer **H** does not create any significant steric strain (as seen from Scheme 7) and hence the *E*-isomers of the products seem not be thermodynamically entirely forbidden. Nevertheless, the addition/elimination alternative still may be operative due to the attractive interactions between the positive and negative charges in the rotamer **G** that retains the Z-configuration of the final products.

The quite different results for the same reaction with acetylenedicarboxylates[22] may be explained by a better distribution of the negative charge over the carboxylic group in the initial zwitterion that makes the anionic site less basic and hence incapable of abstracting a proton from position 2 of the imidazole ring.

The competitive C(2)-vinylation is likely to proceed via the concordant 3,2-stereoselective migration (without loss of stereochemistry) of the 1-phenyl-2-cyanoethenyl group in the intermediate **E**[24,25] (Scheme 8).

In summary, we have disclosed that the three-component reaction between 1-substituted imidazoles, alkyl- and arylisocyanates, and cyanophenylacetylene proceeds at room temperature under non-catalytic and solvent-free conditions to afford *N*-(*Z*)-alkenylimidazole-2-carboxamides in up to 72% yields. A particular synthetic advantage of the reaction is its complete *Z*-stereoselectivity. The reaction is accompanied by a minor competitive C(2)-vinylation of the imidazole ring to give (*Z*)-2-(2-cyano-1-phenylethenyl)imidazoles in trace to 37% yields. In view of the high pharmacological importance of imidazoles bearing carboxamide functions, the novel representatives of this series synthesized with *N*-cyanoethenyl substituents are attractive precursors for targeted drug design. The exploratory results obtained spread further the frontiers of the new rapidly developing concept for functionalization of the imidazole scaffold, which is based on zwitterion/carbene intermediates, the adducts of imidazoles with electron-deficient acetylenes.

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Supplementary data

Supplementary data (Experimental procedures for the preparation of compounds **4a**–**h** and their spectroscopic characterization) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.10.049.

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