A Metal-Free, Three-Component Manifold for the C2-Functionalization of 1-Substituted Imidazoles Operating 'On Water'

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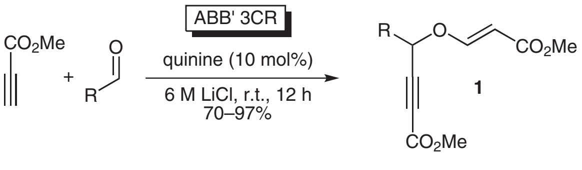
Abstract: A metal-free, three-component process for the C2-functionalization of N-alkylated imidazoles is reported The multicomponent manifold operates under 'on water' conditions through the formation of a water-stable (permanent) nucleophilic imidazole carbene (imidazolium ylide). Whereas the incorporated vinyl ether functionality is a convenient handle for further chemical manipulation of the functionalized heterocycle (complexity generation), the use of water as the reaction media gives it a bonus of added benefits in terms of safety, bench-friendly processing and environmental care.

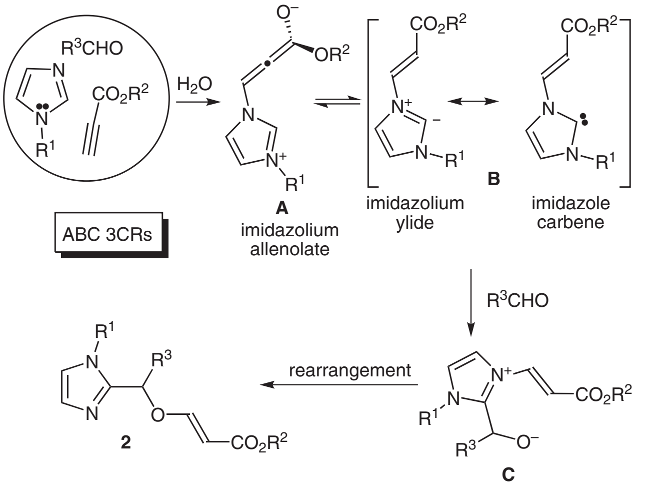
Key words: nitrogen heterocycles, carbenes, ylides, multicomponent reactions, water

A recent contribution from the Trofimov's group[1] describing a novel three-component C2-functionalization of 1-substituted imidazoles under solvent-free conditions prompted us to report our own results with the 'on water'[2] version of such multicomponent reaction. Some years ago, we started a wide research program aimed to the design and development of efficient domino synthetic manifolds based on the catalytic generation of allenolate ions by the reaction of a good nucleophile (tertiary amine or phosphine) and a terminal conjugated alkyne.[3] We have described elsewhere[4] that when these allenolate ions are generated under 'on water' conditions and in the presence of an aldehyde, they afford propargyl enol ethers **1** via a chemo-differentiating ABB′ 3CR[5] manifold (Equation 1), which operates with higher efficiency than the corresponding organic homologues. Based on these results, we explored the possibility to functionalize 1-substituted imidazoles[6] via the allenolate-driven multicomponent manifold outlined in Scheme 1.



Equation 1

It was expected that the N-substituted imidazole triggered the multicomponent process by the nucleophilic addition on the terminal alkynoate to generate the corresponding imidazolium allenolate **A**, which would be basic enough to transfer the reactivity from the chain (allenolate) to the ring (C2-ylide) via a 1,5-prototropic rearrangement. In the presence of an aldehyde, the imidazolinium ylide (imidazole carbene)[7] intermediate **B** would generate the corresponding zwitterionic alkoxide adduct **C**, which in turn would rearrange to the final product **2**, restoring the aromaticity at the heterocyclic ring. Overall, this three-component reaction would constitute a convenient and metal-free manifold to the C2-functionalization of N-substituted imidazoles[8] 'on water'. To the best of our knowledge, there are no precedents for such a multicomponent manifold operating under 'on water' conditions.



Scheme 1 Three-component C2-functionalization of N-substituted imidazoles 'on water'

In this communication we report our results on the development of this multicomponent manifold, which parallel those reported by Trofimov et al. in the absence of solvent.[1] Importantly, our results show that nucleophilic imidazole carbenes (imidazolium ylides) can be conveniently formed and handled under 'on water' conditions to functionalize the parent heterocyclic ring at the C2-position. The use of water as the supporting media ensures a bonus of practicability and safety to these highly exother-

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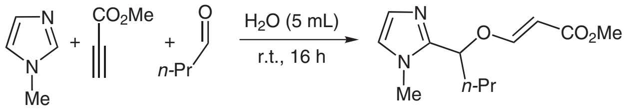
mic processes in relation to their solvent-free counterparts.

We undertook this study with the implementation of the reaction of *N*-methylimidazole, methyl propiolate, and butyraldehyde under 'on water' conditions (Equation 2, Table 1). Among the different stoichiometries assayed for this multicomponent reaction, that one shown in entry 5 proved to be the most effective in terms of chemical efficiency (61%) and atom economy (2:3:1 ratio). Temperature was an important reaction factor with a detriment effect on the reaction yield (compare entries 2 and 3). Finally and not less important, the order of addition of the reagents proved also to be significant. The addition order: alkynoate, N-alkylated imidazole and aldehyde showed to be the best and it was used in further experiments.



2a

Equation 2

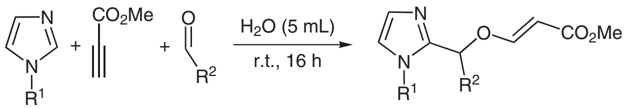
Table 1 Multicomponent C2-Functionalization of *N*-Methylimidazole

Entry	NMI[a] (equiv)	$HCCCO_2Me$ (equiv)	*n*-PrCHO (equiv)	Temp (°C)	Yield (%)[b]
1	2	1	1	r.t.	17
2	2	1	3	r.t.	6
3	2	1	3	40	3
4	1	2	1	r.t.	40
5	2	3	1	r.t.	61

[a] NMI = *N*-methylimidazole.

[b] Isolated and pure compound.

Once a practical set of reaction conditions was found for this multicomponent reaction, we began to explore its scope and generality, using *N*-methyl and *N*-butylimidazoles as representative examples of N-alkylated imidazoles featuring different lipophilicity. We select a set of aldehydes spanning a convenient spectrum of lipophicity and reactivity and methyl propiolate as the only source of the required alkynote (Equation 3, Table 2).[10] In general, the reaction was general for both aliphatic and aromatic aldehydes, with a general better efficiency for the more lipophilic aldehydes (compare entries 9–13 with entries 1–4, 7, and 8). An unexpected subtle influence of the lipophilicity of the N-alkylated imidazole was observed. We found an erratic relationship between the aldehyde and imidazole lipophilicities and the reaction efficiency (compare entries 1, 2 with 3, 4 and 7,8). The low stereoselectivity of this three-component reaction was something more than surprising and unexpected from our own experience on multicomponent processes involving β-onium acrylates and alkoxide ions, which used to be stereoselective (*E*-isomer).



2 R^1 = Me
3 R^1 = Bu

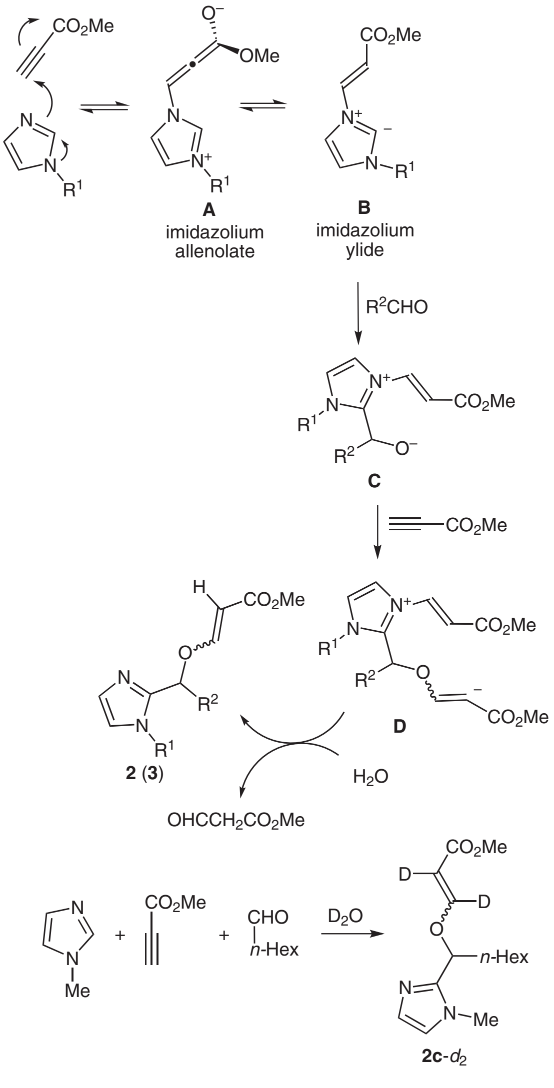
Equation 3

Table 2 Multicomponent C2-Functionalization of N-Substituted Imidazoles

Entry	R^1	R^2	Product	Yield (%)[a]	*E*/*Z*
1	Me	*n*-Pr	**2a**	63	3:2
2	Bu	*n*-Pr	**3a**	30	3:2
3	Me	Et	**2b**	28	3:2
4	Bu	Et	**3b**	61	3:2
5	Me	*n*-Hex	**2c**	70	3:2
6	Bu	*n*-Hex	**3c**	53	3:2
7	Me	*i*-Pr	**2d**	30	3:2
8	Bu	*i*-Pr	**3d**	66	3:2
9	Me	*c*-Hex	**2e**	50	3:2
10	Bu	*c*-Hex	**3e**	90	3:2
11	Me	Ph	**2f**	74	3:2
12	Bu	Ph	**3f**	55	3:2
13	Bu	$4\text{-}O_2NC_6H_4$	**3g**	75	3:2

[a] Isolated and pure compound.

Trofimov et al. also reported low stereoselectivities in their solvent-free reaction of *N*-methylimidazole and different aldehydes when methyl propiolate was used as the alkyne source.[1] This low stereoselectivity seemed to us to be related with a bimolecular route from the alkoxide **C** to the final product **2** (**3**), via the zwitterionic intermediate **D** (Scheme 2). The alternative intramolecular version for this rearrangement (alkoxide addition–imidazole elimination) was expected to be stereoselective, mainly affording the *E*-isomer. A piece of evidence for this bimolecular mechanism came from the reaction of heptanal, methyl propiolate, and *N*-methylimidazole in D_2O (Scheme 2). The reaction afforded derivative **2c**-d_2 in low yield (15%) and stereoselectivity (*E*/*Z* = 3:2), with deuterium incorporated at both positions of the enol double bond (see Supporting Information). Whereas this pattern for deuterium incorporation was difficult to explain from an intramolecular rearrangement from **C** to **2** (**3**), it was the expected result from the mechanistic picture outlined in Scheme 2, if the reversible addition of *N*-methylimidazole on the alkynoate is slow enough to allow a fast H–D alkynoate exchange. If this was the case, deuterated alkynoate should be incorporated into intermediate **D**, placing a deuterium atom at the β-position of the acrylate unit in the final product **2c**. Deuteration of this intermediate **D** with D_2O should account for the second incorporation of deuterium in **2c**. The low efficiency of this reaction in D_2O could be related with major isotopic effects operating at this step (a net O–D bond is broken in this step).[9]



Scheme 2 A mechanistic proposal for the multicomponent C2-functionalization of N-alkylated imidazoles with aldehydes and alkynolates

In summary, we have reported a metal-free, three-component process for the C2-functionalization of N-alkylated imidazoles. The multicomponent manifold operates under 'on water' conditions through the formation of a water stable (permanent) nucleophilic imidazole carbene (imidazolium ylide). This carbene is alkylated by a cascade process involving an efficient carbene–aldehyde addition, alkoxide–alkynoate addition, and protonation and hydrolysis set of consecutive reactions. The incorporated vinyl ether functionality is a convenient handle for further chemical manipulation of the functionalized heterocycle (complexity generation). The use of water as the reaction media gives to this manifold a bonus of added benefits in terms of safety, bench-friendly processing, and environmental care.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(2) On water refers to the reactions performed with sparingly soluble or insoluble reactants in water. See: Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2005**, *44*, 3275.

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(5) Chemo-differentiating ABB′ 3CRs refer to three-component reactions that utilize two different components (A and B) to give a product which incorporates into its structure one unit of component A and two chemo-differentiated units of component B (B and B′). For full details and more examples of this type of multicomponent reactions, see: Tejedor, D.; García-Tellado, F. *Chem. Soc. Rev.* **2007**, *36*, 484.

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(7) For previous examples of metal-free C2-substitution of N-substituted imidazoles via nucleophilic carbenes, see: (a) Zificsak, C.; Hlasta, D. J. *Tetrahedron Lett.* **2005**, *46*, 4789. (b) Deng, Y.; Hlasta, D. J. *Org. Lett.* **2002**, *4*, 4017. (c) Deng, Y.; Hlasta, D. J. *Tetrahedron Lett.* **2002**, *43*, 189. (d) Hlasta, D. J. *Org. Lett.* **2001**, *3*, 157.

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(9) In addition to this cause, chemical and physical factors such as differences in viscosity between H_2O and D_2O may affect droplet size and consequently the efficiency of the reaction. For a discussion, see: Jing, Y.; Marcus, M. R. A. *J. Am. Chem. Soc.* **2007**, *129*, 5492.

(10) **General Procedure for the Multicomponent Functionalization of *N*-Alkyl Imidazoles 'on Water' – Preparation of Compound 2c**
To a 250 rpm stirred round-bottomed flask charged with H_2O (5 mL) were sequentially added (order is important) methyl propiolate (0.3 mmol), *N*-methylimidazole (0.2 mmol) and *n*-heptanal (0.1 mmol). An aqueous suspension was inmediately formed which was further stirred at 1000 rpm during 16 h at r.t. The resulting heteroegeneous mixture was extracted with CH_2Cl_2 (3×), and the collected organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography (EtOAc–hexanes, 40:60) gave pure derivative **2c** (70%) as yellow oil. (*E*)-**2c**/(*Z*)-**2c** = 3:2. IR ($CHCl_3$): ν = 1714, 1643, 1445, 1172 cm^{-1}.
(*E*)-**2c**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.49 (d, $^{3}J_{H,H}$ = 12.4 Hz, 1 H), 6.93 (br d, $^{3}J_{H,H}$ = 1.2 Hz, 1 H), 6.80 (br d, $^{3}J_{H,H}$ = 1.2 Hz, 1 H), 5.32 (d, $^{3}J_{H,H}$ = 12.4 Hz, 1 H), 5.05 (dd, $^{3}J_{H,H}$ = 7.8 and 6.6 Hz, 1 H), 3.62 (s, 3 H), 3.61 (s, 3 H), 2.10–1.95 (m, 2 H), 1.43–1.36 (m, 1 H), 1.32–1.18 (m, 7 H), 0.83 (t, $^{3}J_{H,H}$ = 7.0 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.8, 160.2, 144.6, 127.6, 122.6, 98.8, 77.9, 50.9, 33.2, 33.0, 31.4, 28.7, 25.3, 22.4, 13.9 ppm.
(*Z*)-**2c**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.94 (s, 1 H), 6.85 (s, 1 H), 6.58 (d, $^{3}J_{H,H}$ = 7.0 Hz, 1 H), 5.15 (t, $^{3}J_{H,H}$ = 7.3 Hz, 1 H), 4.83 (d, $^{3}J_{H,H}$ = 7.0 Hz, 1 H), 3.77 (s, 3 H), 3.64 (s, 3 H), 2.18–2.10 (m, 1 H), 2.07–1.98 (m, 1 H), 1.36–1.21 (m, 8 H), 0.84 (t, $^{3}J_{H,H}$ = 7.0 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.1, 156.6, 144.5, 123.6, 120.7, 98.5, 78.1, 50.9, 35.3, 33.8, 31.4, 28.7, 24.9, 22.9, 13.9 ppm. MS (70 eV): *m/z* (%): = 281 (0.7) $[M + 1]^+$, 280 (2) $[M]^+$, 179 (100), 213 (16), 195 (17), 180 (63), 135 (34), 125 (10), 122 (11), 121 (24), 110 (10), 109 (53), 108 (15), 107 (41), 96 (84), 95 (65), 81 (11), 55 (12), 54 (15). Anal. Calcd (%) for $C_{14}H_{22}N_2O_3$; C, 64.26; H, 8.63; N, 9.99. Found: C, 64.29; H, 8.76; N, 10.12.