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A novel Zn-catalyzed hydroamination of propargylamides: a general synthesis of di- and tri-substituted imidazoles†

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Starting from commercially available amines and propargylamides a variety of substituted imidazoles were synthesized *via* a novel hydroamination–cyclization sequence. The target compounds are obtained in good to excellent yields in the presence of catalytic amounts of zinc triflate.

Substituted imidazoles represent a common scaffold in numerous bio-active compounds.[1] For example, they act as inhibitors of serotonin 5-HT2B receptors[2] and glutaminyl cyclase,[3] and as antagonists of endothelial differentiation gene (EDG-1),[4] melanocortin 4 (MC4-R)[5] and histamine H_3 receptors.[6] Furthermore, they are known ligands for $GABA_A$ receptors,[7] and selective blockers of an NMDA (*N*-methyl-D-aspartate)-receptor subtype.[8] Representatives of the well known 5-alkylsubstituted imidazoles are cimetidine (**1**), which is used under the trade name *Tagamet* for treatment of heartburn, peptic ulcers, the imidazole alkaloid (**2**),[9] used for cancer treatment, and the naturally occurring alkaloid pilocarpine (**3**), which is a cholinergic agonist and useful in the treatment of glaucoma or xerostomia (Fig. 1).

In addition, imidazoles are widely used as precursors of *N*-heterocyclic carbenes,[10a] organocatalysts,[10b,c] and ionic liquids.[10d] Because of the importance of this class of compounds their synthesis and functionalization reactions have been intensively studied and continue to be an actual subject in organic synthesis. The different synthetic methods for the synthesis of imidazoles can be categorized in two main types: (a) construction of an imidazole core by cyclization protocols, and (b) selective functionalization of the existing imidazole core.[11a–c] Most conventional methods for the synthesis of functionalized imidazoles require several reaction steps, sometimes harsh reaction conditions, expensive catalysts and might be limited in terms of substrate accessibility, generality and diversity. Therefore, the development of novel approaches for the preparation of imidazoles remains a challenging and interesting topic for organic synthesis.

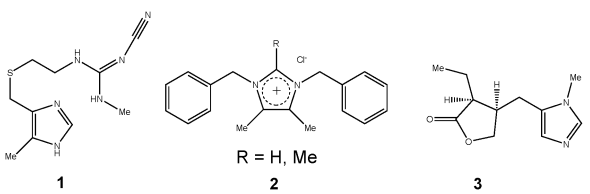

Fig. 1 Cimetidine (**1**), imidazole alkaloid (**2**) and pilocarpine (**3**).

Here, we report a new, general and straightforward synthesis of 2,5(4)-disubstituted and 1,2,5-trisubstituted imidazoles starting from commercially available amines and easily accessible propargylamides using catalytic amounts of zinc triflate.

Until to date, only few examples of using alkynes for the synthesis of imidazoles have been reported.[12] More specifically, Yura described the preparation of imidazole from halo-acetylenes and guanidine.[12h] Eloy and co-workers reported the condensation of propargylamine with imidoesters, imidoyl chlorides and amidines to give substituted imidazoles in moderate to good yields.[12c,d]

Moreover, palladium-catalyzed cyclizations of *N*-propargylbenzamidine and aryl halides led to imidazoles.[12a] Finally, the cyclization of acetylenic ureas to imidazolidinones[12g] or imidazolones has been described.[12e]

There are also limited examples reported for the regioselective ring formation of 1,2,5-trisubstituted imidazoles.[13] Known procedures involve (a) the addition of aminoalcohols to thioamides and subsequent oxidation with PDC,[13a] (b) cycloaddition of thioamides with imines,[13c] and reactions of (c) *N*-monosubstituted amidines with 2-halo-3-alkoxy-2-propenals,[13b] (d) enamines[13d] or silyl enol ethers[13f] with *N*-aryl-*N*′-chlorobenzimidine, (e) α-bromophenylacetaldehyde with isothiosemicarbazones,[13e] and (f) *N*-tosylmethylimines with aldimines.[13g] Obviously, all these approaches are rather special or require the use of unusual reagents.

For some years we have been interested in alkyne hydroamination reactions,[14,15] more recently especially Zn-catalyzed syntheses towards indoles.[16] Based on this work, we investigated the hydroamination reaction of *N*-benzoyl propargylamine with primary aliphatic amines in the presence of zinc salts. To our surprise instead of the expected imine, we obtained *N*-butyl-2-phenyl-5-methyl imidazole as the major product. Apparently, the initial hydroamination reaction is

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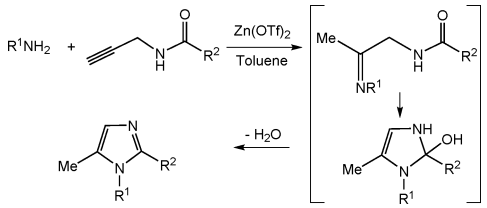


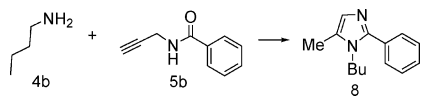
Scheme 1 Zn-catalyzed reaction of *N*-acylpropargylamides and amines.

followed by a Zn-promoted intramolecular cyclization and dehydration reaction (Scheme 1).

Preliminary experiments showed that this novel reaction sequence took place either by conventional thermal heating or under microwave irradiation. Because the microwave-assisted synthesis led to reduction of reaction time and suppression of side products, we performed most of the optimization experiments under the latter conditions. Notably, the success of the cyclocondensation reaction is strongly dependent on the selection of the Zn-source, its amount, temperature, and solvent. In Table 1 selected results of the influence of critical parameters on our model reaction using *N*-benzoylpropargylamine (**5b**) and *n*-butylamine (**4b**) are shown. Optimal results are observed using 5 mol% of $Zn(OTf)_2$ in toluene at 140 °C.

Next, the optimized reaction conditions were used to demonstrate the scope and limitations of our protocol. All amines (**4a–j**) are commercially available. Propargylamides (**5a–g**) were readily synthesized from propargyl amine and suitable acylchlorides using known one step multigram procedures.[17] As shown in Table 2, a variety of primary amines and acylated propargylamines gave the desired products (**6–18**) in good to excellent yields (Table 2). Functional groups like alkyloxy, hydroxyl, halogen, and olefins are well tolerated (Table 2, entries 4, 5, 7, 8, and 10). Both aromatic and aliphatic amines react equally well and give in some cases nearly quantitative yield of the corresponding imidazole (Table 2, entries 3–5). Moderate to good yields were

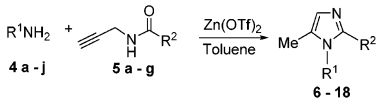
Table 1 Selection of reaction conditions for our benchmark reaction[a]



Entry	Zn source	Catalyst (mol%)	Solvent	T/°C	Time/h	Conv. [%]	Yield[b] [%]
1	$Zn(OTf)_2$	5	Toluene	140	1	100	95[c]
2	$ZnCl_2$	5	Toluene	140	1	94	38
3	$ZnBr_2$	5	Toluene	140	1	84	23
4	$Zn(ClO_4)_2$	5	Toluene	140	1	86	64
5	$Zn(OTf)_2$	5	Dioxane	120	1.5	86	62
6	$Zn(OTf)_2$	5	Heptane	120	1.5	91	65
7	$Zn(OTf)_2$	5	THF	100	1.5	18	3
8	$Zn(OTf)_2$	5	CH_2Cl_2	80	1.5	20	1
9	$Zn(OTf)_2$	15	Toluene	100	1	55	35
10	$Zn(OTf)_2$	10	Toluene	120	1	83	74
11	$Zn(OTf)_2$	5	Toluene	130	1	98	85
12	$Zn(OTf)_2$	3	Toluene	140	1	95	86
13	TfOH	5	Toluene	140	1	24	4

[a] Reaction conditions: alkyne (0.25 mmol), amine (1.5 eq.), solvent (1 mL), 100 W, microwave irradiation. [b] GC yield. [c] Isolated yield.

Table 2 Reaction of propargylamides with aromatic and aliphatic amines to functionalized imidazoles[a]



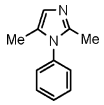
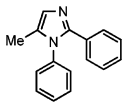
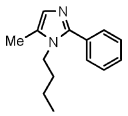
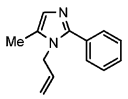
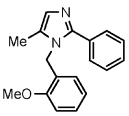
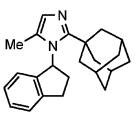
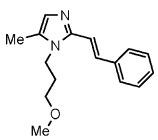
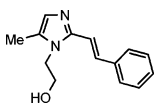
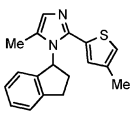
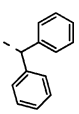
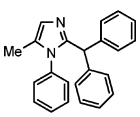
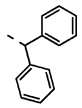
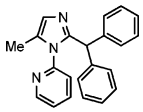
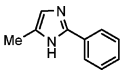
Entry	Amine		R^{2b}		Product		Yield[c] [%]
1		**4a**	Me	**5a**[17d]		**6**[18]	73
2		**4a**		**5b**[17d]		**7**[12d,13f]	87
3		**4b**		**5b**		**8**[12d]	95
4		**4c**		**5b**		**9**	96
5		**4d**		**5b**		**10**	96
6		**4e**		**5c**[17d]		**11**	78
7		**4f**		**5d**[17d]		**12**	81
8		**4g**		**5d**		**13**	55
9		**4e**		**5e**		**14**	78
10		**4h**		**5f**[17b]		**15**	38
11		**4a**		**5g**[17e,g]		**16**	61

Table 2 (*continued*)

Entry	Amine	R[2b]	Product	Yield[c] [%]
12	 **4i**	 **5g**	 **17**	43
13	NH_3 **4j**	 **5b**	 **18**[19]	91

[a] Reaction conditions: alkyne (0.5 or 1 mmol), amine (1.5 eq.), toluene (1 or 2 mL), 140 °C, 1 h, 100 W, microwave irradiation. [b] Dashed line points out the bond position to carbonyl group and to imidazole. [c] Isolated yield.

observed in the case of halogenated aromatic amine **4h**, heteroaromatic amine **4i** and sterically hindered systems (Table 2, entries 10–12). Moreover, we were able to show the generality of our approach for the synthesis of 2,5(4)-disubstituted imidazoles. Here, the method was successfully used with gaseous ammonia instead of amines in an autoclave to yield the desired imidazole **18** in 91% yield (Table 2, entry 13). Thus, our approach allows for regiospecific introduction of various substituents into the imidazole ring just by choosing the proper combination of starting materials.

In conclusion, we have developed a new, effective one-step approach for the synthesis of 2,5(4)-disubstituted and 1,2,5-trisubstituted imidazoles from commercially available amines and propargylamides. These reactions constitute the first examples of Zn-catalyzed one-pot synthesis of imidazoles. Advantageously, a broad tolerance of various functional groups is observed and the targeted products were obtained in good to excellent yields as stable solid compounds.

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