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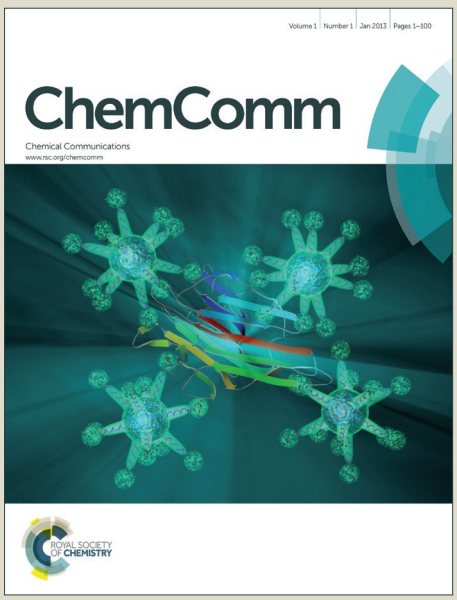

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Copper-mediated C(sp^3)-H azidation with Me_3SiN_3: synthesis of imidazoles from ketones and aldehydes

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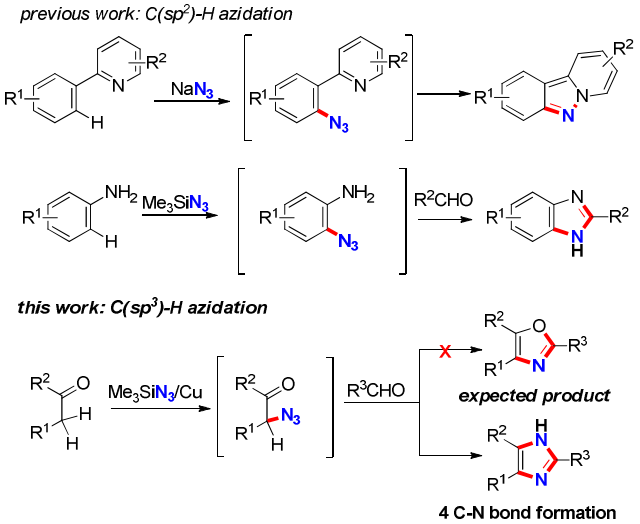
An efficient construction of 2,4,5-trisubstituted imidazoles, through copper-mediated three-component reaction involving ketones, aldehydes, and Me_3SiN_3, has been developed. During the process, 4 C-N bonds were formed sequentially. Experimental results and DFT calculations suggested that azidation of the alpha methylene group of ketone was the key C-N bond-forming step.

In recent years, transition-metal-catalyzed direct C-H bond amination/amidation has been intensively studied due to the great importance of nitrogen-containing compounds in almost all areas of chemical research.[1] In terms of nitrogen sources, non-activated N-H free amines/amides under oxidative conditions or pre-activated N-X species in the absence of oxidant are normally applied.[2] Organic azide is increasingly used as an alternative nitrogen source in directing group assisted intermolecular C-H amination/amidation catalyzed by Rh,[3] Ir,[4] Ru,[5] Co,[6] Pd,[7] and Cu,[8] in which N_2 gas is generated as the only byproduct under oxidant-free conditions.[9] Besides, functionalized organoazide is also applied in intramolecular C-H amination/amidation, which offers a new approach for the construction of N-heterocycles. For instance, a variety of N-heterocycles including pyrroles, indoles, carbazoles, and benzoimidazoles were accessed starting from vinyl- or arylazides, developed by Driver et al.[10] Alternatively, N-heterocycles could also be constructed through one-pot sequential C-H azidation/amination using organic or inorganic azide followed by intramolecular C-N or N-N bond formation. By using this strategy, Jiao et al developed an efficient synthesis of pyrido[1,2-*b*]indazoles via tandem C(sp^2)-H azidation and denitrogenative N-N bond formation co-catalyzed by Pd and Fe (Scheme 1).[11a] The same group also developed a novel Cu-catalyzed anilinic NH_2 directed C(sp^2)-H azidation to afford 2-azido-anilines which could be further transformed to benzimidazoles with aldehydes.[12a] However, synthesis of N-heterocycles through azidation of C(sp^3)-H bond was scarce in literature.[13] Herein, we report a copper-mediated three-component reaction for the synthesis of 2,4,5-trisubstituted imidazoles involving ketones, aldehydes, and Me_3SiN_3. Unlike our recent report on the construction of imidazo[1,5-*a*]pyridines through amination of benzylic C(sp^3)-H bond,[14] azidation of the *Alpha* C-H bond of ketone was proposed as the initial C-N bond-forming step, which was supported by experimental results as well as DFT calculations (Scheme 1). In this reaction, imidazole rather than the expected oxazole was obtained, and two nitrogen atoms were introduced from Me_3SiN_3 by four C-N bonds formation.

The scaffold of imidazole exists in many natural products and pharmaceutical agents with broad biological activities, such as antimicrobial, anti-neoplastic, anti-anxiety, and anti-inflammatory and consequently, much attention has been paid to their synthesis.[15] The synthesis of densely substituted imidazoles is mainly focused on three-component condensation of 1,2-diketones, aldehydes, and ammonia or modification of existing imidazole core by transition-metal-catalyzed cross-coupling reactions.[16] However, developing a general procedure for imidazole synthesis starting from readily available substance is still desirable.



Scheme 1. C-H azidation for the construction of N-heterocycles.

Continuing our interest in heterocycle synthesis with azide,[8a-b,14] we initiated the study by reacting 1,2-diphenylethanone **1a** with *p*-methylbenzaldehyde **2a** in the presence of Me_3SiN_3 under the reaction conditions we reported recently.[14] To our surprise, an imidazole derivative **3a**, rather than the expected oxazole product, was isolated in 32% yield

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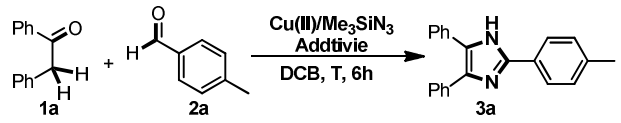
(entry 1, Table 1). Control experiments indicated that the copper salt was essential and PivOH was important for this transformation (entries 2-3). Screening of copper species and acids revealed that the initial use of $Cu(TFA)_2xH_2O$ and PivOH was the best combination (entries 6-11). It was notable that when the reaction was performed in air or O_2, the formation of **3a** was completely inhibited, and 1,2-diketone, the oxidation product of **1a**, was isolated as the major byproduct. Considering this side reaction, the amount of **1a** was increased, and as a result, the isolated yield of **3a** was slightly improved (entry 12). When a solution of Me_3SiN_3 in DCB was introduced to the reaction mixture via a syringe pump during 1.25 h, the yield of **3a** was improved significantly to 61% (entry 13). Finally, the novel imidazole synthesis reached a satisfactory level when 1.2 equiv of $Cu(TFA)_2xH_2O$ was used (82%, entry 14). It was noteworthy that no by-product, derived from either Schmidt reaction[17] or Jiao's reaction[18] through C-C bond cleavage, was detected.

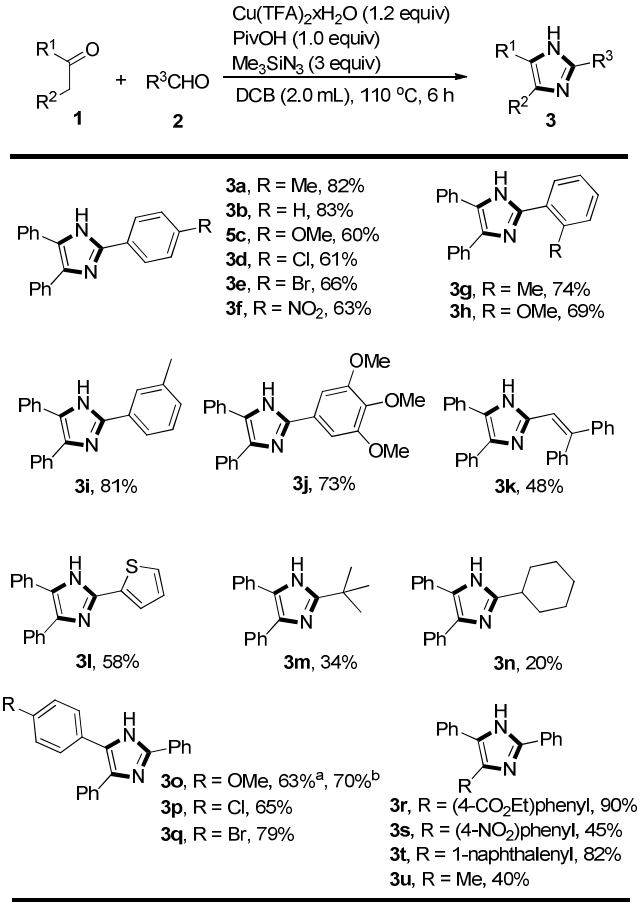
Table 1. Optimization of the reaction condtions.[a]



entry	Copper salts (eq.)	Additive (1.0 eq)	**1a/2a**	Yield[b]
1	$Cu(TFA)_2xH_2O$ (1.0)	PivOH	1/1	32 %
2	No copper salt	PivOH	1/1	n.d.
3	$Cu(TFA)_2xH_2O$ (1.0)	No acid	1/1	21%
4[c]	$Cu(TFA)_2xH_2O$ (1.0)	PivOH	1/1	trace
5[d]	$Cu(TFA)_2xH_2O$ (1.0)	PivOH	1/1	n.d.
6	$Cu(OAc)_2$ (1.0)	PivOH	1/1	trace
7	$CuCl_2$ (1.0)	PivOH	1/1	trace
8	CuI (1.0)	PivOH	1/1	trace
9	$Cu(TFA)xH_2O$ (1.0)	TFA	1/1	21%
10	$Cu(TFA)xH_2O$ (1.0)	TsOH	1/1	trace
11	$Cu(TFA)xH_2O$ (1.0)	PivOH	1/1	trace
12	$Cu(TFA)xH_2O$ (1.0)	HOTf	2/1	34%
13[e]	$Cu(TFA)xH_2O$ (1.0)	PivOH	2/1	61%
14[e]	**$Cu(TFA)xH_2O$ (1.2)**	**PivOH**	**2/1**	**82%**
15[e]	$Cu(TFA)xH_2O$ (1.2)	PivOH	1.5/1	54%
16[e]	$Cu(TFA)xH_2O$ (1.2)	PivOH	2.5/1	65%

[a] Reaction conditions: **1a** (0.2-0.5 mmol), **2a** (0.2 mmol), DCB (2 mL), 110 °C under Ar for 6 h. [b]Yields of isolated product. [c] At 100 °C for 24 h. [d] In O_2 (balloon). [e] A solution of Me_3SiN_3 in 0.5 mL of DCB was injected via a syringe pump during 1.25 h, then the mixture was stirred for 4.75 h. DCB = *o*-dicholorobenzene. PivOH = pivalic acid. TFA = trifuloro acetic acid. TsOH = *p*-methybenzeneosulfonic acid. HOTf = trifluoromethanesulfonic acid.

With the optimal reaction conditions in hand, the scope of both aldehydes and ketones containing α-methylene moiety was studied (Scheme 2). Benzaldehydes substituted with either electron-donating OMe or electron-withdrawing Cl, Br, NO_2 in the *para* position reacted smoothly with **1a** to provide the corresponding imidazoles **3c-3f** in 60-66% yields. The oxidatively labile 3,4,5-trimethoxybenzaldehyde also survived the reaction (**3j**, 73%). In addition, substituents in the *ortho* position of benzaldehydes did not affect the product formation (**3g**, **3h**), suggesting that the reaction was not sensitive to the electronic nature nor the steric hindrance of aldehyde. 3,3-Diphenylacrylaldehyde and thiophene-2-carbaldehyde were also compatible with the reaction conditions, delivering 2-vinylimidazole **3k** and 2-thiophenylimidazole **3l** in 48% and 58% yields, respectively. Notably, aliphatic aldehydes could afford the corresponding alkylated imidazoles (**3m**, **3n**) as well, albeit in lower yields (20-34%). Next, reactions of benzaldehyde with diverse substituted acetophenones were investigated. 1-Aryl-2-phenylethanones substituted with *para*-OMe, Cl, or Br groups reacted smoothly to furnish 2,4,5-triaryl imidazoles **3o-3q** as mixtures of tautomers in good yields, which showed good functional group compatibility. Besides, 1-phenyl-2-arylethanones substituted with electron donating (*para*-OMe) and electron withdrawing (*para*-ester) groups gave the corresponding products in good yields (**3o, 3r**). However, a NO_2 group in the same position gave the corresponding product **3s** in a lower yield of 45%. In addition, propiophenone could also be served as the reaction partner, giving **3u** in synthetically useful yield.



Scheme 2. Substrate Scope. Reaction conditions: **1** (0.4 mmol), **2** (0.2 mmol), PivOH (0.2 mmol), $Cu(TFA)_2.xH_2O$ (0.24 mmol), DCB (2.0 mL) and Me_3SiN_3 (0.6 mmol, 3.0 equiv), a solution of Me_3SiN_3 in 0.5 mL of DCB was injected via a syringe pump during 1.25 h, then the

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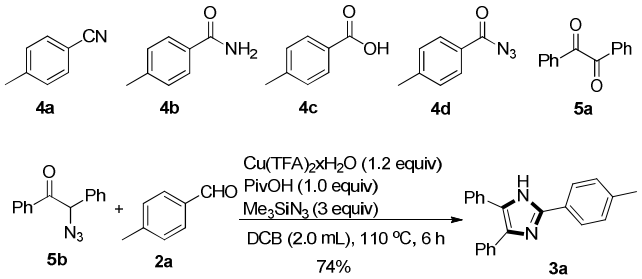
mixture was stirred stirred for 4.75 h, 110 °C, in argon. [a] Starting from 1-(4-methoxyphenyl)-2-phenylethanone. [b] Starting from 2-(4-methoxyphenyl)-1-phenylethanone.

To gain insights into the reaction mechanism, several possible intermediates derived from *p*-methylbenzaldehyde **2a** were investigated in reactions with 1,2-diphenylethanone **1a** under the same reaction conditions (Scheme 3). First, 4-methylbenzonitrile **4a**, a potential intermediate from Schmidt reaction of **2a** in the presence of Me_3SiN_3 and acid, was tested. However, only 1,2-diketone **5a**, an oxidation product of **1a**, was detected together with unconsumed **1a** and **4a**. Similar phenomena were observed with 4-methylbenzamide **4b**, 4-methylbenzoic acid **4c**, or 4-methylbenzoyl azide **4d** as reactants in place of aldehyde **2a**, ruling out the possibility of their being reaction intermediates (Scheme 3). Reaction of 1,2-diketone **5a** with aldehyde **2a** failed to lead to the formation of **3a**. When 2-azido-1,2-diphenylethan-1-one **5b** was subjected to the standard reaction with **2a**, the expected imidazole **3a** was isolated in 74% yield. It is known that copper salt can promote the transformation of ketone or aldehyde to its imine derivative in the presence of azide.[19] Therefore, azidation of the methylene group in 1,2-diphenylethanone or its imine intermediate is proposed as the key step in the current imidazole synthesis. However, direct amination of the methylene group, similar to our recent report on the synthesis of imidazo[1,5-*a*]pyridine through benzylic C(sp^3)-H bond amination,[14] cannot be ruled out. To confirm that C(sp^3)−H azidation product **5b** was a plausible reaction intermediate, density functional theory (DFT) calculations were conducted.[20]



Scheme 3. Investigation of possible reaction intermediates.

In conclusion, we developed an efficient method for the synthesis of tri-substituted imidazoles starting from simple acetaphenone derivatives and aldehydes, which are readily available. In this process, two nitrogen atoms derived from Me_3SiN_3 were formally inserted to the target molecule by 4 C-N bonds formation. Azidation of the sp^3 hybridized C-H bond is the key step for this multiple C-N bond-forming sequence, suggested by experimental results and DFT calculations.

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