



Heterocycle Synthesis

Access to Imidazole Derivatives by Silver(I) Carbonate Mediated **Coupling of Vinyl Azides with Secondary Amines**

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Abstract: An efficient protocol for the synthesis of structurally diverse imidazoles by Ag₂CO₃-mediated coupling of vinyl azides with secondary amines was developed, and 22 different examples were synthesized in good to high yields. This operationally

Introduction

Developing newer, cleaner and more efficient synthetic methodologies for valuable heterocycles is an ever present challenge in organic chemistry. The imidazole ring structure is found in a large number of synthetic and natural products of medicinal importance.^[1] Imidazole-containing molecules have been reported to possess a plethora of biological activities such as antiplasmodium,^[2] antitumor,^[3] antifungal,^[4] antibacterial,^[5] and of being inhibitors of p38 MAP kinase^[6] and B-Raf kinase.^[7] Consequently, a many efforts have been focused on the development of newer synthetic strategies for this privileged scaffold.^[8] In this context, we recently developed a visible-light photoredoxcatalyzed synthesis of imidazoles by coupling of vinyl azides with secondary amines.^[9a] The reaction was found to be highly moisture-sensitive, and imidazoles were obtained in moderate yields (35-71 %). We, therefore, continued our efforts to develop an air- and moisture-tolerant protocol for the efficient coupling of vinyl azides with secondary amines to access imidazoles in high yields.

Given our interest towards developing newer synthetic transformations,^[9] we report herein a straightforward protocol to access structurally diverse imidazoles by Ag₂CO₃-mediated coupling of vinyl azides with secondary amines. It is worth to note that the synthetic strategy described herein involves functionalization of sp³ C-H bonds adjacent to the secondary nitrogen atom. Ag₂CO₃ is a mild oxidant and has long been used in organic synthesis such as Koenigs-Knorr reactions^[10] and Fétizon oxidations.^[11] In recent years, it was successfully utilized as

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simple synthetic strategy allows the formation of three new C-N bonds by cascade reactions that involve sp³ C-H functionalization.

a co-catalyst or oxidant for numerous challenging transformations.^[12]

Vinyl azides 1 are vital three-atom synthons to construct diverse and complex nitrogen heterocycles.^[9e,13] They are known to decompose readily into 2H-azirines 2 under thermal or photochemical conditions.^[13] We envisioned that the 2H-azirines 2 might be attacked by secondary amines 3 to generate intermediates 4, which should undergo ring opening and cyclization to yield intermediates 7 that might be oxidized to imidazoles 8 by using a suitable oxidant (Scheme 1).



Scheme 1. Proposed synthesis of imidazoles 8 by coupling of vinyl azides 1 with secondary amines 3.

Results and Discussion

In order to check the feasibility of the concept, coupling of vinyl azide 1a with 1,2,3,4-tetrahydroisoquinoline 3a was studied under various conditions (Table 1). The reaction did not give the desired imidazole 8a with several catalyst and oxidant combinations such as Cul/H₂O₂, Cul/TBHP, AgOTf/TBHP, MnO₂, DDQ, and PhI(OAc)₂ (Table 1, Entries 1–6). However, we were pleased to obtain high yields (91 %) of imidazole 8a using 150 mol-% of Ag₂CO₃ as an oxidant/catalyst (Table 1, Entry 8). Use of 100 mol-% of Aq₂CO₃ (Table 1, Entry 7) and 50 mol-% of Aq₂CO₃ along with an external oxidant (Table 1, Entry 14) gave lower yields

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of imidazole **8a**. Among several solvents screened, toluene was found to be the best in terms of product yield and purity (Table 1, Entries 12–13). Heating of the reaction mixture in toluene to reflux gave a lower yield of the product, presumably due to the increased side reactions at elevated temperatures (Table 1, Entry 10). The reaction remained incomplete at 60 °C in toluene, even after 24 h, and gave a low yield of imidazole **8a** (Table 1, Entry 11). The reaction also worked well under nitrogen, but the yield of imidazole **8a** was lower by using 150 mol-% of Ag₂CO₃ (Table 1, Entry 15). However, by using a higher loading of Ag₂CO₃ gave high yields of imidazole **8a**, even under nitrogen (Table 1, Entry 16). It indicated that atmospheric oxygen supported the reaction when 150 mol-% of Ag₂CO₃ was used (Table 1, Entry 8).

Table 1. Coupling of vinyl azide ${\bf 1a}$ with 1,2,3,4-tetrahydroisoquinoline ${\bf 3a}$ to yield imidazole ${\bf 8a}.^{\rm [a]}$



[a] Reaction conditions: vinyl azide **1a** (0.5 mmol), 1,2,3,4-tetrahydroisoquinoline **3a** (0.5 mmol), catalyst/oxidant, solvent (5 mL), stiring in open air, 12 h. TBHP = *tert*-butyl hydroperoxide, n.d. = desired product not detected by TLC. [b] Isolated yields. [c] The reaction was run for 24 h. [d] The reaction was carried out under nitrogen.

Having optimized reaction conditions at hand (Table 1, Entry 8), we tried to explore the scope of the Ag_2CO_3 -mediated coupling of vinyl azides and secondary amines to yield imidazoles. Vinyl azides **1a–1j** and **1m** were obtained by Knoevenagel condensations of phenacyl azides with aldehydes, whereas vinyl azides **1k–1l** were obtained from the corresponding styrenes (for details, see the Supporting Information). A number of vinyl azides derived from aromatic aldehydes bearing halogen atoms and electron-withdrawing functional groups gave very high yields (90–95%) of the desired imidazole derivatives (Table 2, Entries 1–2, 6, 9–10, 19 and 21). Vinyl azides derived from electron-rich aromatic aldehydes, heteroaromatic aldehydes and aliphatic aldehydes gave relatively lower yields (68–

Table 2. Scope of the imidazole synthesis by coupling of vinyl azides ${\bf 1}$ with secondary amines ${\bf 3}.^{\rm [a]}$





Table 2. (Continued).



[a] Reaction conditions: vinyl azide 1 (0.5 mmol), amine 3 (0.5 mmol), Ag₂CO₃ (0.75 mmol), toluene (5 mL), 90 °C, stiring in open air, 12 h. ^[b] Isolated yields.



81 %) of the imidazole derivatives (Table 2, Entries 3–5, 7, 8, 11 and 20). Lower yields of the imidazoles with these vinyl azides might be correlated with the increased side reactions of the 2*H*-azirines derived from such azides. Vinyl azides derived from styrene gave very high yields (91–95 %) of the desired imidazole derivatives (Table 2, Entries 12–14). Vinyl azides derived from phenacyl azides bearing halogen atoms, electron-withdrawing as well as electron-releasing functional groups worked well leading to high yields of the imidazoles (Table 2, Entries 4–11 and 19–21).

In terms of secondary amines, the reaction gave high yields of the imidazoles **8** with 1,2,3,4-tetrahydroisoquinoline **3a** and 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **3b** (Table 2, Entries 1–14 and 19–21). The reaction also worked well and gave high yields (79–81 %) of the desired imidazoles by using *N*-benzylanilines **3c** and **3d** (Table 2, Entries 15–17). However, it gave relatively lower yields (65 %) of imidazoles by using dibenzylamine (**3e**) (Table 2, Entry 18).

In order to demonstrate the synthetic competence of our synthetic strategy, a gram-scale (5 mmol) synthesis of **8a** was performed. Compound **8a** was obtained in 90 % yield in the gram-scale reaction, and we could regenerate 80 % of the Ag₂CO₃ used in the reaction according to a literature procedure.^[14] The regenerated Ag₂CO₃ was used for further reactions, which showed the same catalytic efficiency as the fresh one.

Next, we carried out a control experiment whereby a mixture of vinyl azides 1m and amine 3a was heated in toluene in the absence of Aq₂CO₃ (Scheme 2). The reaction proceeded smoothly to yield a product the structure of which was tentatively assigned as **9a** (rather than **7**; see Scheme 1) by analyzing its ¹H and ¹³C NMR spectra. Formation of compound **9a** can be explained by a plausible mechanism depicted in Scheme 2. Treatment of crude 9a with Ag₂CO₃ gave the desired imidazole 8t in 90 % yield. Formation of imidazole 8t from 9a can be explained by considering an Ag₂CO₃-mediated oxidation of the tert-amine to iminium ion 10a.[15] The intermediate 10a is attacked by the neighboring amine (NH₂) to yield another intermediate 11a, which is further oxidized to the final product 8t. Ag₂CO₃ was found to be very crucial for the success of the imidazole synthesis as other oxidants such as MnO₂ oxidized 9a to a complex mixture in which 4-methoxybenzoic acid could be isolated after careful purification. Attempts to isolate intermediate 11a by carrying out the reaction under nitrogen were unsuccessful. It was probably oxidized to imidazole 8t during the workup process. 2H-Azirines 2 containing a carbonyl group are very reactive compounds; however, some of them (such as 2n) can be isolated after thermolysis of vinyl azide 1n. Control reactions suggested that Ag₂CO₃ does not interfere in the thermal decomposition of the vinyl azide 1n (Scheme 3). Ag₂CO₃mediated oxidation of 1,2,3,4-tetrahydroisoquinoline led to a mixture of products in which 3,4-dihydroisoguinoline (12) and 3,4-dihydroisoquinolin-1(2H)-one (13) were characterized as major components (Scheme 4). These experiments suggest the possibility of an alternative mechanism for the formation of imidazoles 8 as depicted in Scheme 5. The 2H-azirine 2 is attacked by 3,4-dihydroisoquinoline (12) to generate an intermediate 14, which rearranges to a dihydroimidazole 15. The







Scheme 2. Control experiments of vinyl azide 1m with amine 3a and mechanistic rationalization for the formation of imidazole 8t.

dihydroimidazole **15** is oxidized to the final product **8** under the reaction conditions.



Scheme 3. Thermal decomposition of vinyl azide 1n to 2H-azirine 2n with and without Ag_2CO_3 .



Scheme 4. Oxidation of 1,2,3,4-tetrahydroisoquinoline with Ag₂CO₃.



Scheme 5. Proposed mechanism for the Ag_2CO_3 -mediated coupling of 1,2,3,4-tetrahydroisoquinoline **3a** with vinyl azide **1** to yield imidazole **8**.

Conclusions

We have developed a straightforward methodology for the synthesis of fused imidazoles by Ag_2CO_3 -mediated coupling of vinyl azides with secondary amines under air- and moisture-tolerant mild reaction conditions. A series of 22 different imidazole derivatives were synthesized in high yields by using the optimized protocol. A few control experiments were carried out to reveal mechanistic details of the reaction.

Experimental Section

Supporting Information (see footnote on the first page of this article): Experimental details and characterization data for the synthesized compounds.

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