Advanced Synthesis & Catalysis

Accepted Article

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To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201700869

Link to VoR: http://dx.doi.org/10.1002/adsc.201700869

UPDATE

DOI: 10.1002/adsc.201((will be filled in by the editorial sttaff**))**

The Base-Promoted Annulation of 2-Hydrazinyl Pyridine and CO_2 toward Triazolones

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Received: ((will be filled in by the editorial staff))

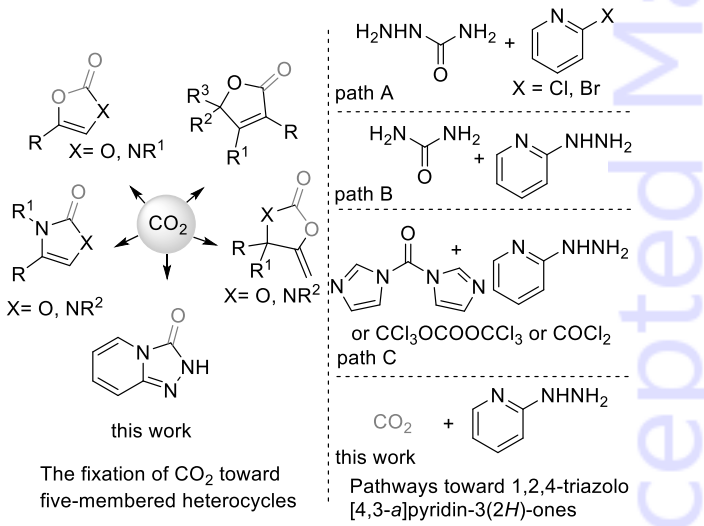
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

Abstract: A base-promoted annulation of 2-hydrazinyl pyridine and atmospheric pressure of CO_2 has been developed in the presence of silane as reducing reagent, affording a series of triazolones in moderate to excellent yields. CO_2 served as a carbonyl source in this transfomation. Moreover, benzamidrazones also worked well under this procedure. Thus, it represents a green, sustainable and straightforward pathway to access triazolone frameworks.

Keywords: carbon dioxide; silane; carbonylation; annulation; base-promoted; triazolones

The fixation of carbon dioxide (CO_2) into value-added organic compounds represents a green and sustainable procure because CO_2 is an economical, renewable and nontoxic C1 source.[1] Some five-membered heterocyclic frameworks, such as cyclic carbonates,[2] lactones,[3] oxazolidinones,[4] and imidazolidones[5] were constructed by this sustainable procedure (left column in Scheme 1). Undoubtedly, from the utilizing CO_2 point of view, the development of new pathway on fixation of CO_2 toward new heterocyclic frameworks would further fulfill the application and chemistry of CO_2.

Triazolones are ubiquitous in a wide range of biologically active molecules and natural products.[6] Being special five-membered ring scaffolds, triazolo[4,3-*a*]pyridin-3(2*H*)-ones are widely considered to be antibacterial, [7] anti-inflammatory,[8] antiviral,[9] antitumour[10] and antiasthmatic agents.[11] Generally, these frameworks were accessed by the annulation of the combination of either 2-hydrazinopyridine and urea[12] or 2-halo pyridine and semicarbazide under high temperature (150-200 °C) in moderate yields.[13] In addition, the toxic phosgene, bis(trichloromethyl) carbonate, and *N*, *N*'-carbonyldiimidazole also served as reaction partners (right column in Scheme 1). [14]



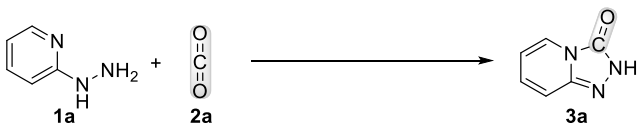
Scheme 1. The fixation of CO_2 toward five-membered heterocycles and pathways leading to triazolones.

We noticed the urea units in triazolones frameworks. This fact as well as our continuous interests on the fixation of CO_2[15] spurred us to test the feasibility of CO_2 as a carbonyl source whereby dearomatization of 2-hydrazinopyridine. [16]

With this regard, we initially tested the reaction of 2-hydrazinopyridine and atmospheric pressure of CO_2 in the presence of 2.0 equivalents of $KHCO_3$ and 5.0 equivalents of $PhSiH_3$ or Et_3SiH in DMF (2.0 mL). However, no reaction took place at all (Table 1,

entries 1 and 2). To our delight, the reaction worked by replacing silane with $HSi(OMe)_3$ (26%, Table 1, entry 3) and $HSi(OEt)_3$ (55%, Table 1, entry 4), respectively. Among the bases tested, Na_2CO_3 increased the yield to 73% (Table 1, entry 5); while K_2CO_3 was the best (84%, Table 1, entries 6). However, strong alkali was not suitable for this transformation (Table 1, entries 7 and 8). Additionally, the reaction efficiency decreased dramatically by either reducing the equivalent of base or conducting the reaction under lower temperature (Table 1, entries 6 and 9). In the absence of either silane or base, no reaction took place (Table 1, entry 9). Other tested solvents, such as dimethylsulfoxide (DMSO), methyl cyanide (MeCN), toluene, and 1,2-dichloroethane (DCE) all resulted in low efficiency or no reaction (Table 1, entry 10).

Table 1. Selected results for screening the optimized reaction conditions.[a]



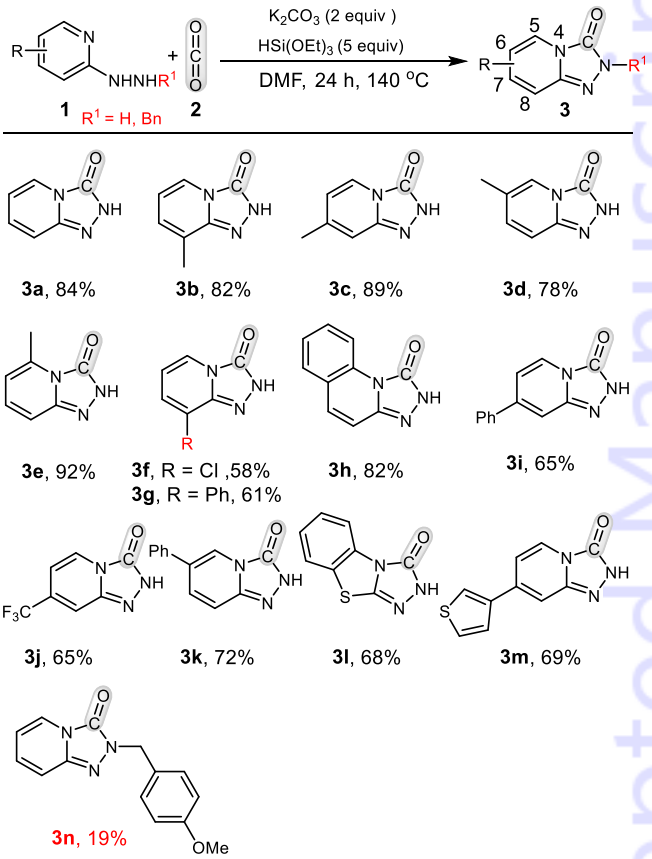
entry	base	silane	yield (%)[b]
1	$KHCO_3$	$PhSiH_3$	n.r.
2	$KHCO_3$	$HSiEt_3$	n.r.
3	$KHCO_3$	$HSi(OMe)_3$	26
4	$KHCO_3$	$HSi(OEt)_3$	55
5	Na_2CO_3	$HSi(OEt)_3$	73
6	K_2CO_3	$HSi(OEt)_3$	84, 23[c], 51[d]
7	Cs_2CO_3	$HSi(OEt)_3$	<10
8	KO^tBu	$HSi(OEt)_3$	trace
9	K_2CO_3	$HSi(OEt)_3$	29[e], 48[f], < 5[g], n.r.[h]
10	K_2CO_3	$HSi(OEt)_3$	<10[i], [j], n.r.[k], n.r[l].

[a] Reaction conditions: 2-hydrazinopyridine **1** (0.2 mmol), base (0.4 mmol), solvent (2.0 mL), CO_2 (1.0 atm), at 140 °C for 24 h, in a sealed Schlenk tube. [b] Isolated yield. [c] base (0.2 mmol). [d] base (0.3 mmol). [e] 120 °C. [f] 130 °C. [g] no base. [h] no silane. [i] DMSO. [j] MeCN. [k] toluene. [l] DCE.

With the optimized reaction conditions in hand, the scope and limitation of substituted 2-hydrazinyl pyridines were studied, as shown in Table 2.

Generally, this procedure was not sensitive to the electronic property of the groups on the pyridine ring as substrates bearing both electron-donating (**3b-3e**, **3g-3m**, 61-92%) and electron-withdrawing groups (**3f**, 58%; **3j**, 65%) all worked well to deliver the annulated products in good to excellent yields. Moreover, the position of substituted groups on the phenyl had almost no effect on the reaction efficiency, as 5- , 6-, 7- and 8- methyl triazolo[4,3-*a*]pyridin-3(2*H*)-ones were isolated in 92% (**3e**), 78% (**3d**), 89% (**3c**) and 82% (**3b**) yields, respectively. To our delight, besides **3b**, substrates possessing an *ortho*-substituents provided the annulation products in acceptable yields (**3f**, 58%; **3g**, 61%). Notably, chloro group, which were handles for potential further functionalization, survived well under this procedure (**3f**). Importantly, 2-hydrazinyl benzothiazole worked well, providing **3l** in 68% yield. Particularly, substrate possessing 3-thiophenyl in pyridine ring ran smoothly, producing **3m** in 69% yield. Surprisingly, 2-(2-(4-methoxybenzyl)hydrazinyl)pyridine **1n** also can react with CO_2 to generate **3n** in 19% yield.

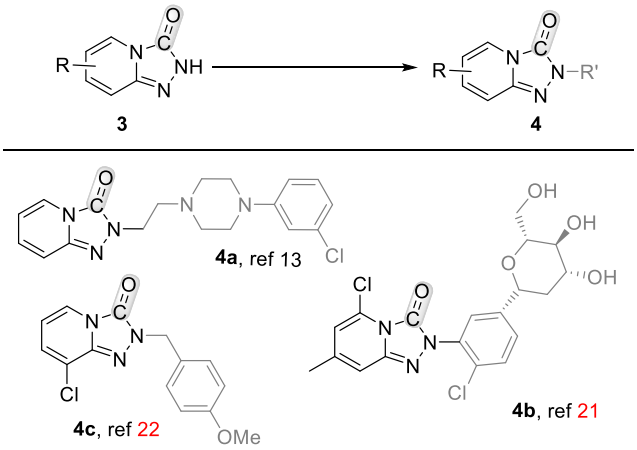
Table 2. Scope of substituted 2-hydrazinyl pyridines. [a]



[a] Reaction conditions: **1** (0.2 mmol), K_2CO_3 (0.4 mmol), $HSi(OEt)_3$ (1.0 mmol), DMF (2.0 mL), CO_2 (1.0 atm), at 140 °C for 24 h, in a sealed Schlenk tube.

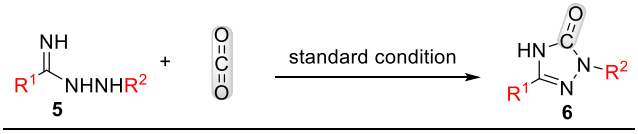
The practicability of this procedure was further increased since **3a** was isolated in an acceptable 70% yield in a 1.0 mmol scale reaction. Moreover, the product triazolone served as precursors to access a series of useful compounds under appropriate conditions (Scheme 2). For example, trazodone **4a**[17] is a novel antipsychotic agent for treating depression in clinic. In Guo's work, **4b** showed potential treatment of type 2 diabetes for its high potency in inhibiting SGLT2.[18] Moreover, **4c** exhibits significant herbicidal activity.[19]

Scheme 2. The further transformation of triazolones.



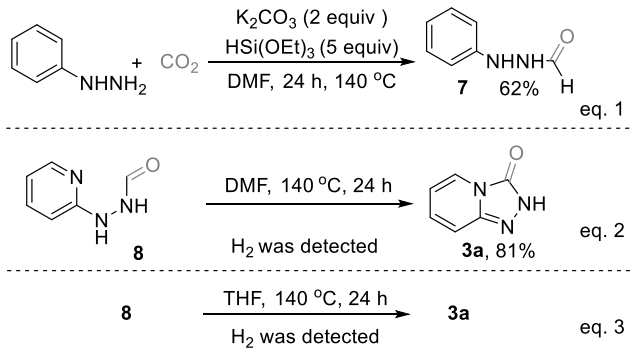
Importantly, this procedure was applicable for benzamidrazone and N^3-phenylbenzamidrazone. The corresponding annulation products **6a-d** were isolated in yields ranging from 42% to 56% yields (Scheme 3). Notably, the annulated products were precursors for antiviral agents,[20] anticonvulsant agents,[21] angiotensin II AT1 receptor antagonists[22] and angiotensin II (AII) antagonists.[23]

Scheme 3. The reaction of benzamidrazone with CO_2.



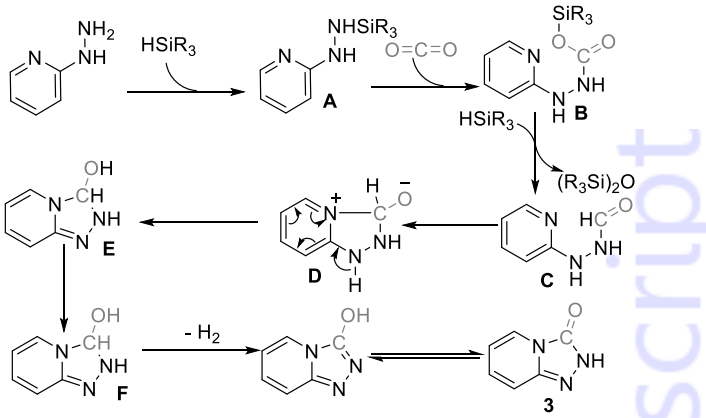
6a, R_1 = Ph, R^2 = H, 42%; **6c**, R^1 = 4-Cl-C_6H_4-, R^2 = Ph, 52%
6b, R^1= Ph, R^2 = Ph, 51%; **6d**, R^1 =4-Me-C_6H_4-, R^2 = Ph, 56%

Scheme 4. Mechanism study



Some control experiments were conducted to gain insights into this transformation. First, phenyl hydrazine was subjected to the standard conditions and the formylated product **7** was isolated in 62% yield, indicating formylated product may serve as an intermediate (Scheme 4, eq. 1). To confirmed it, *N'*-(pyridin-2-yl)formohydrazide **8** was prepared[25] and subjected to the reaction. As expected, it ran smoothly to afford the annulated product **3a** with a comparable 81% yield in DMF under 140 °C even in the absence of silane and K_2CO_3 after 24 h (Scheme 4, eq. 2). Thus, this reaction was likely triggered by the CO_2-mediated formylation. Finally, the extrusion of H_2 was detected during this procedure (Scheme 4, eq. 3, see Supporting Information for details).[24]

Scheme 5. Proposed Mechanism.



Based on these experimental results, a proposed mechanism was outlined in Scheme 5. The reaction is initiated by the reaction of hydrazine pyridine with silane to afford intermediate **A**.[25] Then, the reaction of CO_2 with intermediate **A** produces intermediate **B**, which transforms to hydrazine formyl intermediate **C** after the elimination of silyl ether. Afterwards, the intramolecular nucleophilic attack of nitrogen atom in pyridine ring to carbonyl takes place leading to the cyclized intermediate **D**. Finally, after the transformation of intermediate **D** to intermediate **E**. the aromatization of intermediate **E** delivers the final product **3**, along with the extrusion of H_2 as confirmed in eq. 3 of Scheme 4. The base may be beneficial to the selectivity reduction of CO_2 toward silyl formate by increasing the solubility of CO_2 in the solvent.[26]

In conclusion, we have developed a base-promoted reaction of CO_2 with 2-hydrazinyl pyridine toward triazolones in the presence of silane, where CO_2 served as a carbonyl source. Notably, benzamidrazone and N^3-phenylbenzamidrazone also worked well in this procedure. Thus, this protocol represents an efficient, green and sustainable methodology for incorporation of CO_2 toward heterocycles.

Experimental Section

Annulation toward [1,2,4]triazolo[4,3-*a*]pyridin-3(2*H*)-ones:

A 20 mL of Schlenk tube equipped with a stir bar was charged with 2-hydrazinylpyridines (0.2 mmol, 1.0 equiv),

K_2CO_3 (0.4 mmol, 2.0 equiv), $HSi(OEt)_3$ (1.0 mmol, 5 equiv), DMF (2.0 mL). Then the Schlenk tube sealed with a PTFE cap was charged with CO_2 (1 atm) for three times. The reaction mixture was stirred at 140 °C for 24 h in oil bath. After the completion of the reaction, the mixture was directly evaporated under reduced pressure, and the residue was purified by flash column chromatography on silica gel with petroleum ether-EtOAc (V_1/V_2, 2:1) as the eluent to give the desired products.

Acknowledgements

We thank the National Natural Science Foundation of China (no. 21572025), "Innovation & Entrepreneurship Talents" Introduction Plan of Jiangsu Province, the Key University Science Research Project of Jiangsu Province (15KJA150001), Jiangsu Key Laboratory of Advanced Catalytic Materials &Technology (BM2012110) and Advanced Catalysis and Green Manufacturing Collaborative Innovation Center for financial support. Sun thanks the National Natural Science Foundation of China (no. 21602019) and Young Natural Science Foundation of Jiangsu Province (BK20150263) for financial support.

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10.1002/adsc.201700869

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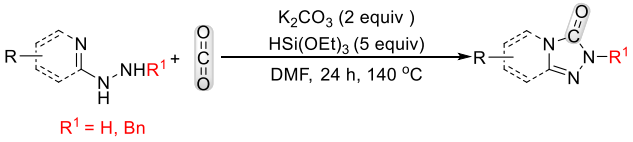

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