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Brønsted Acid-Catalyzed Decarboxylative Redox Amination: Formation of *N*-Alkylindoles from Azomethine Ylides by Isomerization

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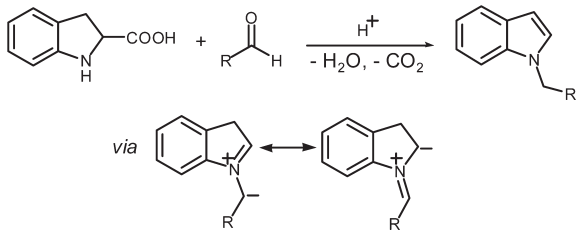
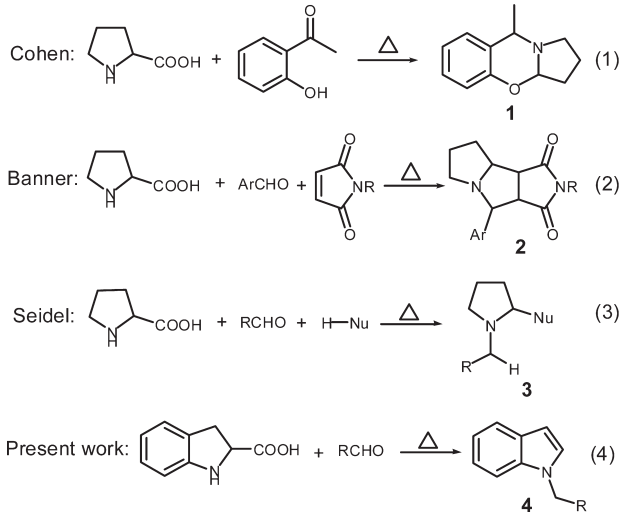
Received November 12, 2010



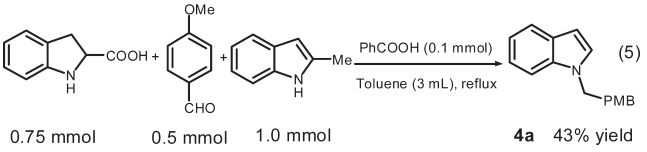
A Brønsted acid-catalyzed decarboxylative redox amination involving aldehydes with 2-carboxyindoline for the synthesis of *N*-alkylindoles is described. The decarboxylative condensations of aldehydes with 2-carboxyindoline produce azomethine ylides in situ, which then transform into *N*-alkylindoles by isomerization.

Decarboxylation of α-amino acids with carbonyl compounds, known as the Strecker degradation, has been extensively studied since it was proposed in 1862.[1] Azomethine ylide was supposed to act as the key intermediate in the process and Grigg had demonstrated this idea exhaustively.[2] In 1979, Cohen reported a reaction involving proline and 2-hydroxyacetophenones to afford **1** (eq 1).[3] Banner designed a MCR of proline, aldehyde, and maleimide for the synthesis of **2** by using an intermolecular [3 + 2] cycloadditions of azomethine ylides with alkene (eq 2).[4] Recently, Seidel described a three-component decarboxylative of amino acids involving a new reaction pathway for azomethine ylides (eq 3).[5] When we investigated the azomethine ylide generated from aldehyde with 2-carboxyindoline, it was interesting to find that it was bound to form *N*-alkylindole **4** by isomerization rather than react with nucleophiles (eq 4).

N-Alkylindoles are very important building blocks not only in biologically active natural products, but also in pharmaceutical compounds.[6] Traditionally, treatment of alkyl halides with indole was a straight method.[7] The requirement of equivalent base and low atom-efficiency restricted the application of this methodology. Recently, transition metal-catalyzed reactions also have become a very powerful tool in this area.[8] Herein, we report a Brønsted acid-catalyzed decarboxylative redox amination for the synthesis of *N*-alkylindoles.



Initially, we were interested in performing a three-component reaction described by Seidel.[5] However, instead of the expected product, the *N*-alkylindole **4a** was isolated with 43% yield (eq 5). Obviously, the reaction between aldehyde with 2-carboxyindoline gave the product **4a** while the nucleophile 2-methylindole did not participate in this process. Since such a decarboxylative redox amination is a potential synthetic method for the formation of *N*-alkylindoles, we tried to further investigate this amination under different conditions.



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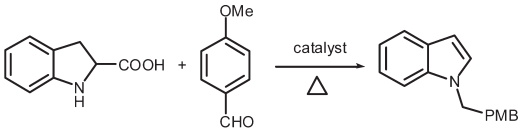
DOI: 10.1021/jo102218v Published on Web 01/18/2011

TABLE 1. Evaluation of Potential Catalyst and Solvent[a]



5 6a 4a

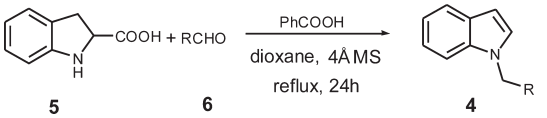
entry	catalyst	solvent	time (h)	**4a** yield[c] (%)
1	—[b]	toluene	24	trace
2	PhCOOH	toluene	24	45
3	PhCOOH	EtOH	24	20
4	PhCOOH	water	30	trace
5	PhCOOH	THF	24	trace
6	PhCOOH	1,4-dioxane	24	67
7	AcOH	1,4-dioxane	24	55
8	TFA	1,4-dioxane	24	60
9	*p*-TsOH	1,4-dioxane	24	50
10[d]	PhCOOH	1,4-dioxane	24	74

[a]All the reactions were conducted with 2-carboxyindoline (1.5 equiv, 0.75 mmol), *p*-anisaldehyde (1 equiv, 0.5 mmol), and catalyst (0.2 equiv, 0.1 mmol) in 3 mL of solvent under reflux in nitrogen atmosphere. [b]No catalyst was used. [c]Isolated yield of the corresponding product. [d]4 Å MS (20 mg) was added.

Treatment of a mixture of 2-carboxyindoline[9] and *p*-anisaldehyde in toluene under reflux in the absence of catalyst afforded little product (Table 1, entry 1). Addition of benzoic acid (0.2 eqiv) to the reaction led to formation of the desired product with 45% yield (Table 1, entry 2). Since the result did not seem so satisfactory, we then began to study the solvent effect, and 1,4-dioxane was found to be the best medium compared with toluene, EtOH, water, and THF (Table 1, entries 2−6). In addition, different Brønsted acids were also evaluated as catalysts for the reaction and benzoic acid was shown to be the optimal catalyst (Table 1, entries 6−9). It was interesting to find that addition of 4 Å MS gave a higher yield (Table 1, entry 10).

With the optimal conditions in hand, we then began to explore the substrate scope of this reaction. As shown in Table 2, a variety of aromatic aldehydes bearing various types of substituents were employed in the reaction to give the corresponding products with moderate to good yields (Table 2, entries 1−15). Notably, the aldehyde substrates with electron-donating groups on the aromatic ring afforded a little lower yields (Table 2, entries 1−5). The benzaldehyde formed *N*-benzylindole with 78% yield (Table 2, enrtry 6). Moveover, the heteroaromatic aldehydes also could react with 2-carboxyindoline with satisfactory yields (Table 2, entries 16−18). Finally, we focused on the reaction of 1-naphthaldehyde and 9-anthraldehyde. To our delight, 69% and 65% yield were obtained, respectively (Table 2, entries 19 and 20). While aliphatic aldehydes were employed, no desired product was observed.

TABLE 2. Decarboxylative Amination of 2-Carboxyindoline with Various Aldehydes[a]

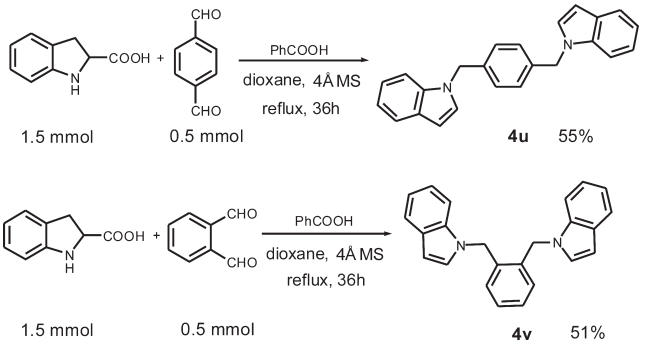


5 6 4

entry	R	**4**	yield (%)[b]
1	4-MeOC$_6$H$_4$	**4a**	74
2	4-MeC$_6$H$_4$	**4b**	70
3	4-N(Me)$_2$C$_6$H$_4$	**4c**	64
4	2-MeOC$_6$H$_4$	**4d**	72
5	2-MOMOC$_6$H$_4$	**4e**	62
6	C$_6$H$_5$	**4f**	78
7	4-FC$_6$H$_4$	**4g**	75
8	2-FC$_6$H$_4$	**4h**	72
9	4-ClC$_6$H$_4$	**4i**	78
10	2-ClC$_6$H$_4$	**4j**	75
11	4-BrC$_6$H$_4$	**4k**	76
12	2-BrC$_6$H$_4$	**4*l***	73
13	4-NO$_2$C$_6$H$_4$	**4m**	82
14	3-NO$_2$C$_6$H$_4$	**4n**	80
15	4-CF$_3$C$_6$H$_4$	**4o**	69
16	2-pyridinyl	**4p**	81
17	2-furanyl	**4q**	79
18	2-thiophenyl	**4r**	80
19	1-naphthyl[c]	**4s**	69
20[c]	9-anthracenyl[c]	**4t**	65

[a]All the reactions were conducted with 2-carboxyindoline (1.5 equiv, 0.75 mmol), aldehyde (1 equiv, 0.5 mmol), PhCOOH (0.2 equiv, 0.1 mmol), and 4 Å MS (20 mg) in 3 mL of 1,4-dioxane under reflux in nitrogen atmosphere. [b]Isolated yield of the corresponding product. [c]2-Carboxyindoline (0.9 mmol) was added.

SCHEME 1. Decarboxylative Redox Amination of Phthalaldehydes



Having established the scope of this reaction, we then turned our attention to the decarboxylative redox amination of phthalaldehydes. It was satisfying to find that *p*-phthalaldehyde and *o*-phthalaldehyde reacted with 2-carboxyindoline (3 equiv) smoothly to afford the corresponding products, albeit with longer time and lower yields (Scheme 1).

According to the reaction results and related research,[2,5] we proposed a mechanism for the decarboxylative redox amination based on the formation of azomethine ylide. As shown in Scheme 2, in the presence of an acid, direct condensation of aldehyde **6** with 2-carboxyindoline **5** produces oxazolidin-5-one **A**,[5] which is subsequently converted to azomethine ylide **B** by releasing one molecular CO_2. Protonation of azomethine ylide results in the formation of the iminium ion pair **C** and **D**. Deprotonation of the

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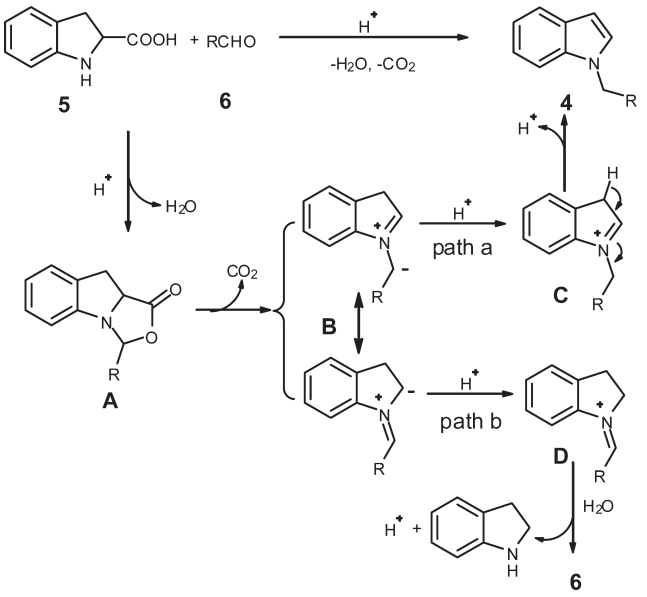
SCHEME 2. Proposed Mechanism for Decarboxylative Redox Amination



intermediate **C** at C-3 directly leads to the formation of final product **4** (path a).[10] Alternatively, hydrolysis of the intermediate **D** produces indoline and regenerates the starting aldehyde (path b). The aromatization is considered to be the orginal motivation of this decarboxylative redox process.

In conclusion, a Brønsted acid-catalyzed decarboxylative redox amination has been developed for the synthesis of *N*-alkylindoles from aldehydes with 2-carboxyindoline. Besides, we also have disclosed a novel mode of reactivity for azomethine ylides, which transform into *N*-alkylindoles by isomerization. Further studies are in progress in our laboratory.

(10) An isotopic labeling reaction also was carried out to support our proposed mechanism. For the detailed information about the isotopic labeling reaction, see the Supporting Information.

Experimental Section

General Procedure for the Synthesis of 4a−t. To a solution of *p*-anisaldehyde (0.5 mmol) and 2-carboxyindoline (0.75 mmol) in 1,4-dioxane (3 mL) were added PhCOOH (0.1 mmol) and 4 Å MS (20 mg) under nitrogen atmosphere. The mixture was stirred at room temperature for 0.1 h and then refluxed for another 24 h. Then the mixture was cooled and purified by flash column chromatography to give the product **4a** as as colorless oil with 74% yield. ^{1}HNMR (DMSO, 500 MHz) δ 7.55 (d, J = 7.8 Hz, 1H), 7.46 (m, 2H), 7.18 (d, J = 8.5 Hz, 1H), 7.10 (t, J = 7.2 Hz, 1H), 7.02 (t, J = 7.1 Hz, 1H), 6.86 (d, J = 8.6 Hz, 2H), 6.46 (d, J = 3.1 Hz), 5.32 (s, 2H), 3.73 (s, 3H). ^{13}C NMR (DMSO, 125 MHz) δ 159.7, 136.7, 131.3,130.0, 129.6, 129.5, 122.2, 121.5, 120.1, 115.0, 111.3, 101.9, 56.1, 49.7. HRMS m/z 238.1229 ([M + H]$^+$), calcd for ([$C_{16}H_{15}NO$ + H]$^+$) 238.1226.

General Procedure for the Synthesis of 4u,v. To a solution of *p*-phthalaldehyde (0.5 mmol) and 2-carboxylindoline (1.5 mmol) in 1,4-dioxane (3 mL) were added PhCOOH (0.1 mmol) and 4 Å MS (20 mg) under nitrogen atmosphere. The mixture was stirred at room temperature for 0.1 h and then heated at reflux for another 36 h. Then the mixture was cooled and purified by flash column chromatography to give the product **4u** as a white solid with 55% yield. Mp 120−122 °C. ^{1}H NMR (DMSO, 500 MHz) δ 7.56 (d, J = 7.7 Hz, 2H), 7.44 (d, J = 3.0 Hz, 2H), 7.40 (d, J = 8.1 Hz, 2H), 7.11 (m, 6H), 7.02 (t, J = 7.5, 7.1 Hz, 2H), 6.47 (d, J = 3.0 Hz, 2H), 5.34 (s, 4H). ^{13}C NMR (DMSO, 125 MHz) δ 138.5, 136.8, 130.1, 129.4, 128.3, 122.3, 121.6, 120.2, 111.2, 102.1, 49.9. HRMS m/z 337.1694 ([M + H]$^+$), calcd for ([$C_{24}H_{20}N_2$ + H]$^+$) 337.1699.

Acknowledgment. Financial support from Natural Science Foundation of China (Nos. 21025207 and 20975092) is greatly acknowledged.

Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.