



Addition of carbamoylsilane to isatins: Highly efficient synthesis of 3-hydroxy-3-aminocarbonyl-2-oxindoles derivatives



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ABSTRACT

The first addition reaction between isatins and carbamoylsilane has been developed which provides 3-hydroxy-3-aminocarbonyl-2-oxindoles core structures with excellent yields. Moreover, the reaction could undergo a one-pot synthesis process to furnish 3-hydroxy-3-aminocarbonyl-2-oxindole with gram-scale.

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Introduction

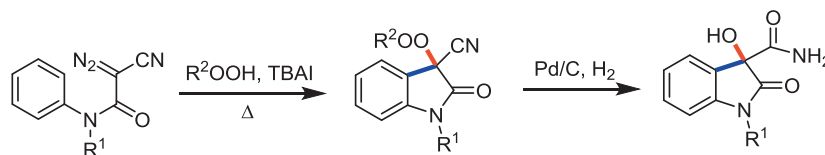
Since the pioneering work of palladium-catalyzed aminocarbonylation reaction discovered by Heck and co-workers in 1974,¹ a great deal of efforts have been made to the development of aminocarbonylation reactions due to the importance of amides played in biological systems as well as in the fields of natural products, pharmaceuticals, chemical industry and polymers.² Among them, amines and carbon monoxide are powerful and most frequently used aminocarbonyl reagents.³ However, these approaches often need to use harsh reaction conditions such as high pressure, high temperature and handling of hazardous carbon monoxide gas.⁴ So the development of new CO-free methods is appealing. In recent years, some CO-equivalents have been developed such as silacarboxylic acids,⁵ formic anhydrides and N-substituted formamides,⁶ alkyl formates⁷ and carbamoylstannanes.⁸ Previously, we successfully realized the efficient preparation of various carbamoylsilanes in excellent yields,⁹ which are environmentally benign reagents and can be employed as amides sources to carry out a series of aminocarbonylation reactions, including the palladium-catalyzed aminocarbonylation of halides,¹⁰ acid chlorides,¹¹ addition of carbamoylsilanes to aldehydes,¹² ketones¹³ and imines.¹⁴ Extending the application of carbamoylsilanes in aminocarbonylation reactions is our ongoing interest.

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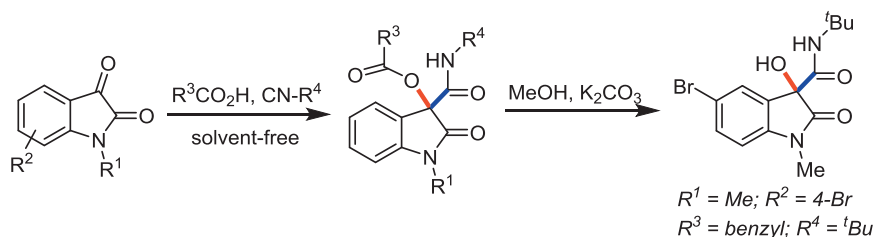
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The 3-hydroxy-3-aminocarbonyl-2-oxindoles subunits are featured in a number of naturally occurring products as well as biologically, pharmaceutically and medically active molecules.¹⁵ As a consequence, finding simple and effective synthetic methods to realize these valuable intermediates draws increasing attention of organic chemists. Studer's group¹⁶ developed one-pot sequence for the synthesis of 3-peroxy-substituted oxindoles from readily prepared 2-cyano-2-diazo-acetamides through cyclization and peroxidation. After another procedure of reduction, 3-hydroxy-3-aminocarbonyl-2-oxindoles could be obtained (Scheme 1). Biju's group¹⁷ demonstrated a three-component Passerini reaction by employing isatins as the carbonyl compound component under solvent-free conditions. The reaction resulted in the synthesis of biologically important 3-hydroxy-3-aminocarbonyl-2-oxindoles in high yields after hydrolysis (Scheme 1). Despite these important achievements, the direct conversion of isatins to aminocarbonyl oxindoles remains an unsolved synthetic problem and direct aminocarbonylation reactions of proper amido-equivalents to isatins is a concise method. So we try to explore the reaction between isatins and carbamoylsilane to construct 3-hydroxy-3-aminocarbonyl-2-oxindoles directly (Scheme 1). To the best of our knowledge, little efforts are concentrated on the synthesis of the core structure and we will describe our progress in this manuscript.

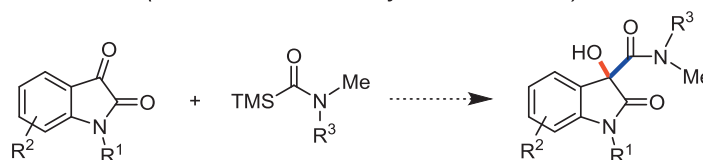
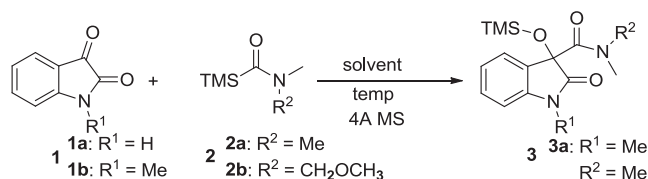
We began our investigation by testing the model reaction between isatins **1** and carbamoylsilanes **2** in benzene at rt (Table 1). R¹-substituted isatins are necessary because no product was observed after 2 h (Table 1, entries 1–2) when active proton



(2). Biju's work (Passerini reaction and hydrolysis)



(3). This work: (direct aminocarbonylation reaction)

**Scheme 1.** Approaches to 3-hydroxy-3-aminocarbonyl-2-oxindoles.**Table 1**Screening of carbamoylsilanes, solvents and reaction conditions for the reactions.^a

Entry	R ¹	R ²	Solvent	Temp [°C]	Time [h]	Yield [%] ^b
1 ^c	H	Me	Benzene	rt	2	0
2 ^c	H	CH ₂ OMe	Benzene	rt	2	0
3 ^c	Me	CH ₂ OMe	Benzene	rt	2	0
4 ^c	Me	Me	Benzene	rt	12	49
5	Me	Me	Benzene	rt	0.5	73
6	Me	Me	CH ₂ Cl ₂	rt	12	38
7	Me	Me	THF	rt	12	33
8	Me	Me	CH ₃ CN	rt	12	12
9	Me	Me	Toluene	rt	1	65
10	Me	Me	Benzene	0	1	62
11	Me	Me	Benzene	40	0.5	83
12	Me	Me	Benzene	60	0.1	91
13 ^d	Me	Me	Benzene	60	0.1	86

^a Unless noted, the reaction was performed on 0.1 mmol scale with **1** (1.0 equiv), **2** (1.5 equiv), 4 Å molecular sieves (25 mg) and solvent (0.5 ml) under inert gas protection and anhydrous condition for displayed time.

^b Yield of isolated product.

^c No 4 Å molecular sieves was used.

^d **2a** (1.2 equiv) was used.

existed in isatin **1a**. We speculated that the competitive desilylative protonolysis of carbamoylsilane has occurred which was found in our previous work.^{14c} The substituent R² on the carbamoylsilane nitrogen atom is a crucial factor. No desired reaction occurred when carbamoylsilane **2b** was used (Table 1, entry 3). Dimethyl substituted carbamoylsilane **2a** provided the desired product **3a** in 49% yield after 12 h at rt and the raw material **1b** could not be

consumed completely (Table 1, entry 4). When 4 Å molecular sieves were added to the reaction system, it improved both the yield and reaction rate because of removing trace amounts of deleterious moisture in the reaction (Table 1, entry 5). When *N,N*-dimethylcarbamoyl(trimethyl) silane **2a** was selected as aminocarbonylation reagent, the reaction conditions were further optimized. Benzene was selected as the optimal solvent in terms

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