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Synthesis of dihydrocarbazoles via (4+2) annulation of donor-acceptor cyclopropanes to indoles

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ABSTRACT

Dihydrocarbazoles were synthesized through a novel [4+2] annulation of donor-acceptor cyclopropanes (DACs) to indoles. This reaction was performed in ethanol by using *para*-toluenesulfonic acid as catalyst. Mechanism of this reaction might involve the following three steps: (i) an electrophilic ring-opening reaction of the DACs with indoles, in which C3 position of indole acts as a nucleophilic site, (ii) an intramolecular dehydration induced ring-closing reaction occurs that offers a spiro intermediate, and (iii) a following 1,2-migration which leading to a dihydrocarbazole scaffold. Otherwise, dihydroisoindole can also be constructed by replacing the indole component with pyrrole as nucleophile.

1. Introduction

Among nitrogen-containing heterocycles, carbazoles have garnered significant attention in the literature because of their presence in various natural products and pharmaceutically relevant compounds. A large number of carbazoles exhibited good biological activity, such as *anti*-HIV, antimicrobial, *anti*-inflammatory, antiviral, antihistamine and antiserotonin, and so on.[1] Some physical scientists paid also their attention to utilize carbazole derivatives because these compounds displayed very promising optoelectronic properties.[2] For these reasons, a lot of efforts have been paid on the synthesis of these privileged heterocycles. The reported synthetic methods can be categorized into the following three routes: (i) metal catalyzed intramolecular C–H amination starting from *ortho*-amino substituted biphenyl derivatives;[3] (ii) Fischer–Borsche synthesis starting from arylhydrazines and cyclohexanones, which involves a condensation under acidic condition and the subsequent aromatization reaction;[4] (iii) construction of the carbazole scaffold using indole as a template.[5] Although numerous protocols have been developed for the synthesis of carbazole derivatives, those methods suffer from limitations of substrate generality, the availability of starting materials,[6] use of expensive catalyst,[7] and harsh conditions.[8] Therefore, the design of improved and environmentally benign approaches that allow for the rapid, cost-effective synthesis of carbazoles from readily available precursors would be highly desired.

Donor-acceptor cyclopropanes (DACs) widely used in organic conversions in recent years because of their unique reactivity.[9] Particularly, ring-opening reactions of DACs with a variety of nucleophiles provided an easy access to numerous functionalized molecules.[10] The reactions of DACs and nucleophiles were characterized generally by the following two steps: (i) attack of nucleophile to the active site of DACs, which provided a stereodefined linear compound;[11] (ii) a following ring-closing reaction, which afforded usually heterocyclic products.[12] While this annulation is readily accomplished with [3+*n*] (*n*=2, 3, 4) manners,[13] [4+*n*] type of reaction is exceedingly rare.[14] Especially, [4+2] annulation of DACs to a nucleophile to form a product with a six-member ring has rarely been reported.[15] On the other hand, simple indoles were widely used as nucleophiles in electrophilic substitution reactions. Because the most reactive site on the indole ring toward electrophilic substitution is C3 position, indole will tend to react at this position, yielding a C3-substituted product under electrophilic substitution conditions. Intriguingly, when C2-unsubstituted indole was used as substrate, after finishing the substitution reaction, C2 position is quite reactive and can act as a nucleophile as well.[16] This made simple indole to be a 1,2-bisnucleophile. Taking a cue from this fact, in this paper, we developed a Brønsted acid-catalyzed novel [4+2] annulation of DACs to some aromatic bis-nucleophiles, such as indoles and pyrroles, which provided

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dihydrocarbazole and dihydroisoindole derivatives in good yields (Fig. 1). A one-pot sequential [4+2] annulation and aromatization reaction was developed as well, with which carbazole derivatives could be synthesized.

annulation and aromatization reaction.[15] There two catalysts were also examined in our reaction, and 78% and 81% yields were obtained when 150 mol % of catalyst was used (entries 17 and 18). Considering the environmental effect and practical usefulness,

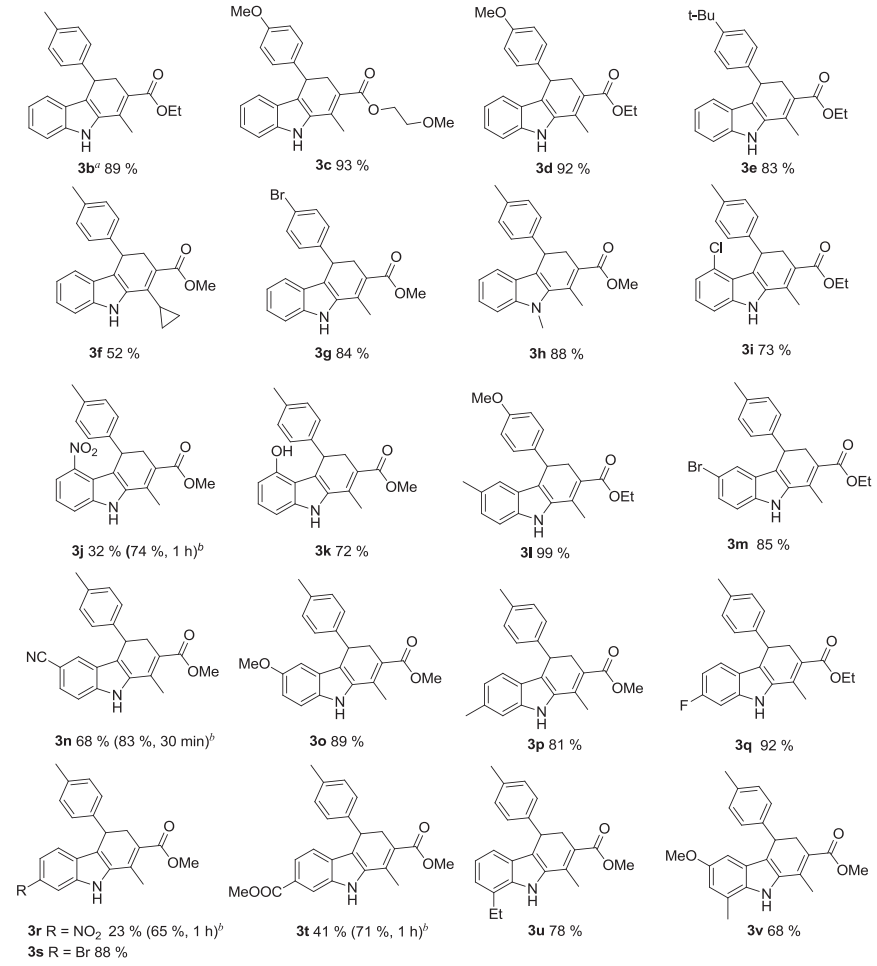

Fig. 1. Substrate scope of the dihydrocarbazole synthesis.

2. Results and discussion

Initial experimentation was undertaken in ethanol using methyl 1-acetyl-2-(*p*-tolyl)cyclopropanecarboxylate **1a** and indole **2a** as substrates. The mixture was heated at 60 °C. No product was formed in the absence of catalyst (Table 1, entry 1). When $CuBr_2$ was used as catalyst, **1a** was consumed rapidly, and a dihydrocarbazole **3a** was isolated from the reaction solution in 55% yield (entry 2). Structure of **3a** has been unambiguously confirmed by the X-ray structural analysis (see ESI).[17] With strong Lewis acids, such as $AlCl_3$, $FeCl_3 \cdot 6H_2O$ and $Sc(OTf)_3$, no significant yield improvement was observed (entries 3 to 5). To our great delight, when *para*-toluenesulfonic acid (PTSA) was used, the yield of **3a** increased to 87% (entry 6). Other Brønsted acids, such as HCl (aqu.) and H_2SO_4, can also be used as catalysts, however, their efficiencies are rather inferior (entries 7 and 8). The effect of solvents on the model reaction was also examined (entries 9 to 14), where ethanol and acetonitrile gave high yields. For safety and environmental reasons, we continued the reactions with ethanol. Further investigation revealed that the reaction was also affected significantly by temperature and catalyst amount (entries 15 and 16). $BF_3 \cdot Et_2O$ and $TiCl_4$ have been used by Ila et al. in a similar sequential [4+2] PTSA/ethanol system is preferred. Finally, the optimal reaction conditions were confirmed to be the followings: 60 °C and 10 mol % of PTSA catalyst. It is noteworthy that this reaction can be finished within 20 min at 60 °C in ethanol solvent, which is quite remarkable. The reaction can also be effectively scaled up with the similar efficiency. For example, the reaction of DAC **1a** (15 mmol) with indole **2a** (15 mmol) gave the corresponding dihydrocarbazole **3a** in 85% yield (4.22 g).

With this optimized reaction conditions in hand, we started to investigate the substrate scope of the [4+2] annulation of DACs to indole. Firstly, the scope of the reaction with respect to DACs was studied (Fig. 1, **3a**–**3g**). It was found that DACs bearing *para*-methyl-, methoxyl-, *tert*-butyl- or bromo-substituted phenyl ring can participate in this reaction readily. The presence of an electron-donating group in the phenyl ring facilitated to some extent progress of the reaction. The DACs with a bulky group generally gave low yields. This steric effect can be verified by the synthesis of **3f**. It should be noted that a dihydrocarbazole **3f** succeeded a cyclopropyl group from the corresponding starting substrate. This group has been demonstrated to be quite active in some organic reactions.[9] Therefore, it may be useful for further functionalization.

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