A Rapid and Efficient Access to Diaryldibenzo[\textit{b,f}][1,5]diazocines

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ABSTRACT

2-Benzoylbenzoyl azides undergo facile cyclization under acidic conditions to give substituted dibenzo[\textit{b,f}][1,5]-diazocines in good yields. This approach shortens the synthetic steps toward these compounds as compared with conventional methods. The mechanism of the diazocine synthesis is assumed to proceed by an unprecedented intermolecular [2 + 2] cyclization.

Dibenzo[\textit{b,f}][1,5]diazocines were first synthesized more than one century ago.\(^1\) The synthesis of this class of compounds has attracted more attention since the 1960s due to the discovery of the hormone-like activity of 2,8-dichloro-6,12-diphenyldibenzo[\textit{b,f}][1,5]diazocine.\(^2\) More recently, material scientists considered them a potential building block for artificial muscles due to their reversible conformational changes occurring during electrochemical redox processes.\(^3,4\)

However, synthetic strategies toward diazocines are quite limited. The most common approach is the condensation reaction of 2-aminobenzophenones, as shown in Scheme 1. This pathway has a few drawbacks: the synthesis of 2-aminobenzophenones either requires tedious protection/deprotection steps\(^5\) of the 2-aminobenzoic acid (route 1) which is atom inefficient or requires expensive 3-arylbenzo[c]isoxazoles (route 2).\(^6–8\) Furthermore, the condensation reaction generally requires a long reflux time and the yield varies dramatically with different substrates and reaction conditions.\(^6,7,9\) The third route involves a Friedel–Crafts acylation of an aromatic ring with 2-isocyanobenzoyl chloride, which further reacts with 2-aminobenzophenones to give unsymmetric 6,12-diaryl-dibenzo[\textit{b,f}][1,5]diazocines (route 3), but in relatively low yields.\(^10\) We herein report a facile synthetic strategy toward dibenzodiazocines which follows a completely different mechanism compared with the reactions mentioned above.

In our efforts to synthesize dibenzodiazocines as a building block for artificial muscles, we initially adopted the conventional 2-aminobenzophenone route. To avoid the protection/deprotection process in the preparation of 2-aminobenzophenone, we envisioned that this precursor could be prepared from 2-benzoylbenzoyl azide via a

Curtius rearrangement. The azide could be made from easily available 2-benzoylbenzoic acid (Scheme 1, route 4).

Hence, 2-(4-bromobenzoyl)benzoic acid 1a was prepared from o-phthalic anhydride and bromobenzene in good yield. The compound was then converted to 2-(4-bromobenzoyl)benzoyl azide 2a in a one-pot reaction and in almost quantitative yield when treated with chloroformate followed by treatment with sodium azide, as shown in Scheme 2. When the pyrolysis of the acyl azide 2a was performed in a mixture of acetic acid and water (volume ratio 1:2), we were surprised to observe the formation of dibenzodiazocine 3a together with the expected 2-amino-benzophenone 4a, although in low yields (Table 1, entry 1). Several other unidentified products were also observed.

More surprisingly, when compound 4a was isolated and resubjected to the same reaction conditions, no formation of dibenzodiazocine 3a was observed even under a prolonged reaction time (Scheme 2).

We then realized that compound 4a might not be the intermediate toward dibenzodiazocine 3a in the pyrolysis process. Compound 4a was clearly the hydrolysis product of an isocyanate intermediate, which was generated from compound 2a via Curtius rearrangement. On the other hand, compound 3 might be formed via a different pathway which was at least not related to, if not hampered by, water. To verify our hypothesis, the reaction conditions were then optimized accordingly, as shown in Table 1.

We first decreased the amount of water in the reaction. When the volume ratio of acetic acid to water was increased from 1:2 to 9:1, the yield of diazocine 3a was increased from 5% to 80% (Table 1, entries 1 to 3), although the yield of aminobenzophenone 4a remained at almost the same level. A further decrease of the water content to 2% suppressed the formation of aminobenzophenone 4a to 7.4% (Table 1, entry 4). When anhydrous glacial acetic acid was used as the solvent, the formation of compound 4a was completely suppressed, with only a slight decrease of the yield of diazocine 3a (Table 1, entry 5). This observation suggested that water was unnecessary for the diazocine synthesis. Compound 4a was again subjected to the same anhydrous AcOH conditions but no 3a formation was observed, suggesting that compound 4a was formed only as a side product. It is worthwhile to note that the formation of diazocine in AcOH was fast; the majority of diazocine was formed in 1 h once the temperature was raised to 80°C, and the reaction time was generally extended to 5 h to guarantee a full conversion.

Reactions in a stronger acid were even faster. The reaction in trifluoroacetic acid (TFA) finished in 2 h and afforded a better yield. More 4a was formed, which might be attributed to the trace amount of water present in TFA (Table 1, entry 6). Triflic acid also worked, but the reaction was too vigorous to handle. Surprisingly, no diazocine was observed when methanesulfonic acid was used as the solvent, which still needed further investigation. Attempts to decrease the amount of acid using a binary solvent system failed, resulting in either a lower yield of diazocine or simply no reaction (Table 1, entries 7, 8), which indicated that an acid environment was necessary for this reaction.
The influence of the substituents on the phenyl ring on the efficiency of cyclization was investigated, as shown in Table 2. Although using TFA as the solvent generally gave better yields, we used AcOH as the solvent in most cases for considerations of toxicity and economic reasons. Phenyl rings bearing electron-donating groups such as methyl and methoxy groups gave better yields (Table 2, entries 4, 5). More electronegative groups such as Cl and NO2 led to lower yields when the reactions were performed in AcOH, but the yields were increased (Table 2, entries 4, 5). More electronegative groups such as methyl and methoxy groups gave better yields (Table 2, entries 4, 5). More electronegative groups such as Cl and NO2 led to lower yields when the reactions were performed in AcOH, but the yields were increased (Table 2, entries 4, 5).

Given that the 2-aminobenzophenone could not afford the corresponding dibenzodiazocine under the reaction conditions chosen, a different mechanism was proposed, as shown in Scheme 3. We assumed that the first step was the Curtius rearrangement, which expelled 1 equiv of N2 and gave the corresponding isocyanate. In the absence of suitable nucleophiles such as water to attack, the resulting isocyanate underwent an intermolecular [2 + 2] cyclization under acidic conditions with the ketone moiety of another molecule to give a highly strained 1,3-oxazetidin-2-one intermediate. The cyclization process might occur in either a stepwise or a concerted manner. The strained intermediate was highly unstable and collapsed to release CO2 to give the desired diaryldibenzodiazocine. This reaction was promoted under acidic conditions, in which the protonation of a carbonyl group might facilitate the cyclization. In the presence of water, the aminobenzophenone formation process competed with this process. Diluted acidic conditions are also unfavorable for diazocine synthesis.

This hypothesis was supported by some experimental evidences. First, the condensation mechanism could be ruled out because it would require 2-aminobenzophenone as the intermediate. As mentioned previously, the failure to convert 2-aminobenzophenone to the corresponding diazocine under the reaction conditions eliminates this pathway. Second, under water-free conditions, we did observe the formation of CO2 during the reaction, which was followed immediately by the diazocine formation (see Supporting Information) and supported the mechanism we proposed.

The mechanism of a [2 + 2] cyclization was also supported by literature precedent. It was reported that phenyl isocyanate underwent [2 + 2] cyclization with excess DMF to form 4-(dimethylamino)-3-phenyl-1,3-oxazetidin-2-one which collapsed and released CO2 to form the imine bond.11 Although 1,3-oxazetidin-2-one intermediates are generally highly unstable, a stable 1,3-oxazetidin-2-one was isolated when methyl isocyanate was reacted with a highly electron-deficient ketone.12 Furthermore, the reaction was promoted either in acidic conditions or in the presence of a fluoride anion, which shows some similarity to our synthesis. A reaction between phthaldehyde and phenyl isocyanate was also reported, which was postulated to go through a 1,3-oxazetidin-2-one intermediate to give N-phenyl-phthalimidine.13 1,3-Oxazetidin-2-one was also prepared by other pathways, and its release of CO2 to form an imine bond at an elevated temperature was confirmed.14

In summary, a rapid and efficient method for the synthesis of diaryldibenzof[b,f][1,5]diazocines was developed. Starting from easily available 2-benzoylbenzoic acid, symmetric diazocines could be prepared in two steps in good yield. The mechanism of the key reaction is plausibly an unprecedented intermolecular [2 + 2] cyclization between an isocyanate and ketone moieties. We are currently exploring further applications of this reaction.

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**Supporting Information Available.** General procedures for the synthesis of diazocines and its precursors, characterization, and spectroscopic data of the key compounds are included. This material is available free of charge via the Internet at http://pubs.acs.org.

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