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Old and New Aryne Precursor, Anthranilic Acid: Multicomponent Reaction of Benzyne with Quinolines or Imines and Pronucleophiles

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An operationally simple and one-pot protocol for the synthesis of a variety of trichloromethylated tertiary amines from anthranilic acid, imines, and chloroform was achieved. This reaction proceeds *via in situ* imine formation followed by the addition of benzyne prepared from anthranilic acid with concomitant proton abstraction of chloroform. By employing this method, a series of β-trichloromethylated anilines were synthesized in moderate to good yields with gram scale. Basic hydrolysis of trichloromethylated dihydoquinoline gave dichloromethylene-1-phenylquinoline in quantitative yield.

Keywords: Benzyne, Imine, Multicomponent reaction
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Arynes are one of the oldest, most interesting and useful intermediates, and powerful reactive electrophiles that have received great attention for the formation of conjugated heterocycles *via* intramolecular cycloaddition.[1] Recent progress of aryne chemistry is mainly due to the aryne precursor, 2-(trimethylsilyl)phenyl triflate (triflate), which produces benzyne under mild conditions (0 ºC to 80 ºC, neutral conditions).[2] This reagent has some advantages on the formation of arynes compared to typical benzyne precursors such as aryl halides, ortho-dihalobenzenes, and diphenyliodonium carboxylate, which generally required harsh reaction conditions (elevated reaction temperature or use of strong base).[1] Due to the low-lying LUMO of benzyne, the neutral nucleophiles add to benzyne generating zwitterions, which are reactive toward the electrophiles or pronucleophiles. For example, Hu *et al.*, Biju *et al.* and Tan *et al.* have reported three-component reaction of aryne derived from triflate with quinolines and pronucleophiles to give the corresponding three-component products.[3] Three-component reactions of arynes with imines, and pronucleophiles (chloroform, acetonitrile, terminal alkynes) to afford the corresponding tertiary anilines were also reported by Tian and coworkers (Figure 1).[4] We have also reported the three-component reaction of arynes with cyclic ethers or imines, and chloroform to afford the corresponding terminal trichloroalkyl phenyl ethers and amines.[5] Generally, these reactions were performed within 1 mmol scale due to the use of expensive triflate derivatives. For this reason, there is no report on the large scale synthesis of three-component reaction. Additionally, fluoride salts such as CsF, KF, and TBAF must be required for the formation of benzyne, which have to remove inorganic byproducts as waste materials that are difficult to recycle. In some cases, 18-crown-6 would be required to solubilize these fluoride sources.[6] Therefore, the development of a simple, inexpensive, and readily available reagent would extend the scope of this transformation.

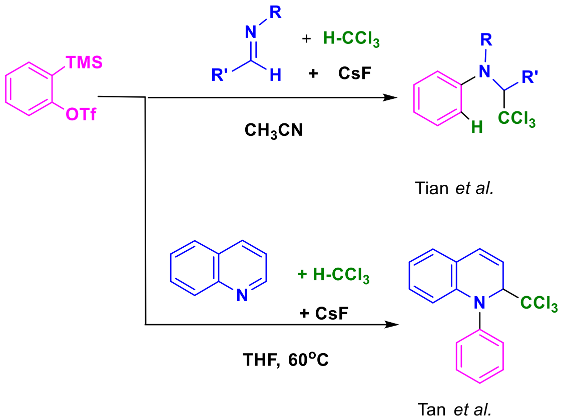


Figure 1. Three-component reaction of triflate, imines, and chloroform

Anthranilic acid **1a**, a typical benzyne precursor, is well known to react with dienes in the presence of alky nitrite to afford the corresponding Diels-Alder adducts in moderate yields.[7] [2+2] or [4+2] Cycloaddition reactions of benzyne derived from benzenediazonium 2-carboxylate with imines were reported: [4+2] cycloaddition of benzyne with benzylideneanilines by Nakayama *et al.*,[8] [2+2] cycloaddition of benzyne with benzylideneanilines by Singal and Kaur,[9] and [4+2] reaction of benzyne with *in situ* formed benzylideneanilines by Shou *et al.* (Figure 2).[10] However, there are relatively few reports on the multicomponent reaction of benzyne starting from anthranilic acid derivatives.[11,12] These results prompted us to investigate the multi-component reaction of several imines containing quinoline derivatives with *in situ* formed benzyne from anthranilic acid and isoamyl nitrite and pronucleophiles whether gram scale synthesis of multi-component products would be accomplished. Since isolated benzenediazonium 2-carboxylate decomposes explosively on being heated or scraped against a hard surface,[13] we have tried the thermal reaction of *in situ* formed benzenediazonium 2-carboxylate with imines, and chloroform.

Three-component reaction products were obtained by the reaction of benzyne prepared from triflate with imines and chloroform[4], whereas, benzylideneaniline **2** react with benzyne prepared from benzenediazonium 2-carboxylate to give [4+2] and [2+2] cyloadducts.[8-10] Thus, we first tried the reaction of benzylideneaniline **2** with *in situ* formed benzenediazonium 2-carboxylate in chloroform whether three-component reaction or [4+2] cycloaddition would proceed.

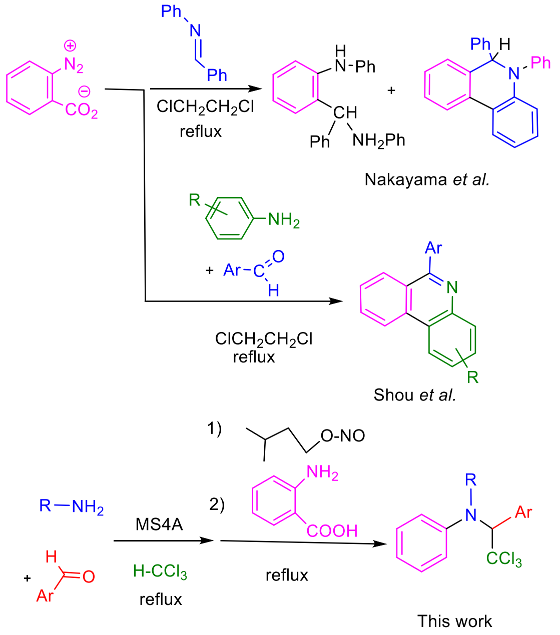
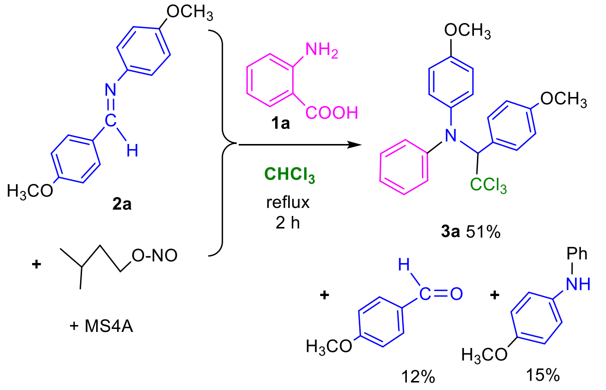


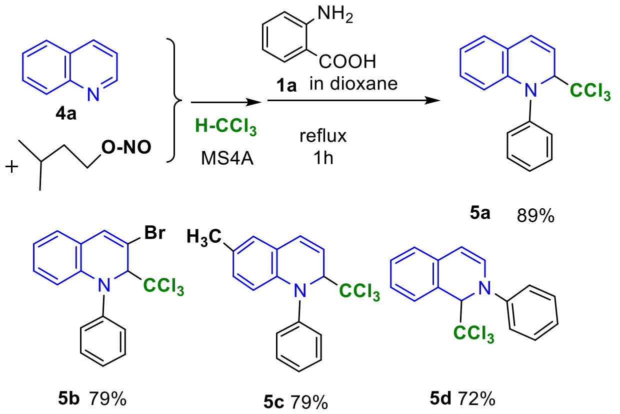
Figure 2. Cycloaddition of benzyne derived from anthranilic acid with benzylideneanilines and this work

Treatment of anthranilic acid **1a** with 4,4'-dimethoxybenzylideneaniline **2a** and isoamyl nitrite in refluxing chloroform resulted in the formation of 4-methoxy-*N*-phenyl-*N*-2,2,2-trichloro-1-(4-methoxyphenyl)ethyl-aniline **3a** in 21% yield. 4-Anisaldehyde (25%) and 4-anisidine (22%) along with unreacted **2a** (15%) were obtained as byproducts, which suggested that *in situ* formed water prevent the reaction to complete. When molecular sieves 4A (MS4A) was added to the solution, aniline **3a** was obtained in 51% yield, which clearly shows that not cycloaddition but three-component reaction proceeded preferentially under these conditions (Scheme 1). Although the yield of **3a** is moderate, compound **1a** found to be a useful and inexpensive precursor for aryne mediated three-component reaction.



Scheme 1. Reaction of **2** with benzyne prepared from anthranilic acid **1a** in chloroform

We then tried the reaction of quinoline **4** with anthranilic acid and chloroform in the presence of isoamyl nitrite whether the corresponding three-component products would be formed. Recently, Tan *et al*. have found that three-component products were obtained by the reaction of quinolines **4** with triflate and chloroform, whereas only 0.15 mmol scale reaction was performed.[14] Treatment of anthranilic acid **1a** in dioxane with quinoline **4a** and isoamyl nitrite in refluxing chloroform resulted in the formation of 2-trichloromethyl-1-phenyl-1,2-dihydroquinoline **5a** in 89% yield. (Scheme 2). Other heterocyclic compounds such as isoquinoline also reacted with benzyne and chloroform to give three-component products **5b-5d** in good yields (Scheme 2).

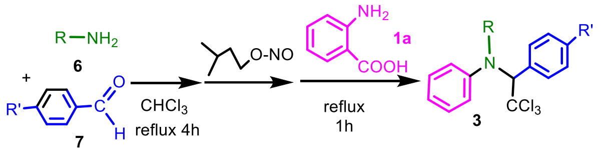


Reaction conditions: **1a** (5 mmol) in dioxane (5 mL), quinoline **4** (3 mmol), MS4A, and chloroform (7 mL), reflux 1 h.

Scheme 2. Reaction of quinoline **4** with benzyne prepared from anthranilic acid **1a** and chloroform

We switched the focus of our investigation to the four-component reaction of primary amines, aromatic aldehydes, with anthranilic acid and chloroform in the presence of isoamyl nitrite. *In situ* formation of imines by the reaction of primary amines with aldehydes were already reported.[4, 15] Treatment of MS4A and *in situ* formed imines from methylamine **6a** and *p*-methylbenzaldehyde **7a** with isoamyl nitrite followed by the addition of anthranilic acid **1a** in refluxing chloroform gave the corresponding four-component product **3b** in 75% yield (Table 1, Entry 1). When *p*-methoxybenzaldehyde **7b** was used, a similar yield of **3c** was obtained in 73% (Entry 2). When butylamine **6b** was used as a primary amine, the four-component products **3d** and **3e** were obtained in moderate yields (Entry 3 and 4). Allyl amine **6c** gave moderate yields of products (Entry 5-6). Benzylamine **6d** gave much better yields of products **3h** and **3i** (Entry 7-8), whereas aromatic aldehydes with electron withdrawing groups at para position gave lower yields of products (Entry 10-12). The present reaction has a broad scope, and various primary amines and aromatic aldehydes can be converted very efficiently into the corresponding trichloromethylated tertiary anilines **3**.

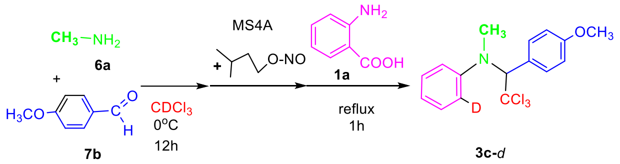
Table 1. Four-component reaction of primary amines **6** with aldehydes **7** followed by the addition of anthranilic acid **1a** in refluxing chloroform



Entry	6		7		3	Yield / %
1	**6a**	R = CH_3	**7a**	R'= CH_3	**3b**	75
2	**6a**	R = CH_3	**7b**	R'= OCH_3	**3c**	68
3	**6b**	R = n-Bu	**7a**	R'= CH_3	**3d**	65
4	**6b**	R = n-Bu	**7b**	R'= OCH_3	**3e**	58
5	**6c**	R = allyl	**7a**	R'= CH_3	**3f**	46
6	**6c**	R = allyl	**7b**	R'= OCH_3	**3g**	42
7	**6d**	R = $PhCH_2$	**7a**	R'= CH_3	**3h**	58
8	**6d**	R = $PhCH_2$	**7b**	R'= OCH_3	**3i**	72
9	**6d**	R = $PhCH_2$	**7c**	R'= H	**3j**	54
10	**6d**	R = $PhCH_2$	**7d**	R'= Cl	**3k**	45
11	**6d**	R = $PhCH_2$	**7e**	R' = Br	**3l**	43
12	**6d**	R = $PhCH_2$	**7f**	R' = F	**3m**	55

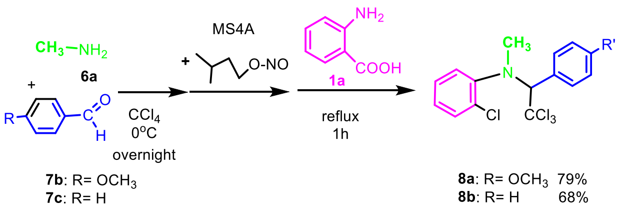
Reaction conditions: **1a** (7.5 mmol) in dioxane (7.5 mL), **6** (5.0 mmol), **7** (5.5 mmol), chloroform (10 mL), and 2.0 g of MS4A, reflux 1 h.

To confirm benzyne insertion to carbon-hydrogen bond of chloroform, the reaction of methylamine **6a** with *p*-methoxybenzaldehyde **7b** in chloroform-*d* followed by the addition of anthranilic acid **1a** in the presence of isoamyl nitrite was carried out. As expected, 93% of deuterated **3c-*d*** was isolated (Scheme 3).



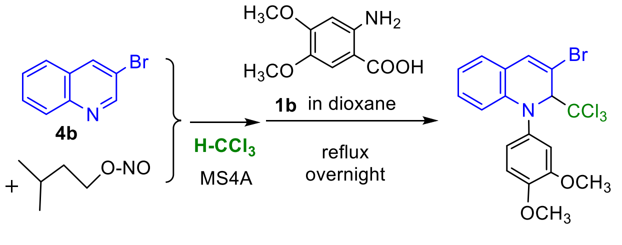
Scheme 3. Reaction of **6a** with **7b** followed by the addition of anthranilic acid **1a** in refluxing chloroform-*d*.

Recently, Yu *et al*. have extended this reaction to the synthesis of ortho-chloroaniline derivatives by using carbon tetrachloride instead of chloroform, which are useful precursors for pharmaceutical products.[16] We have also applied this reaction to the synthesis of ortho-chlorinated phenylation. Treatment of *in situ* formed imine and isoamyl nitrite with anthranilic acid in refluxing carbon tetrachloride resulted in the formation of 2-chlorophenyl derivatives **8a** and **8b** in 79 % and 68 % yields, respectively (Scheme 4). However, when acetonitrile and bromoform were used as pronucleophiles, the corresponding three component products were not obtained.



Scheme 4. Four-component reaction of benzyne with methylamine, aldehyde, and carbon tetrachloride

To confirm substituted anthranilic acid also play as aryne precursor, we then tried the reaction of 2-amino-4,5-dimethoxybenzoic acid **1b** with 3-bromoquinoline in the presence of isoamyl nitrite was carried out. When a solution of anthranilic acid **1b** in dioxane was added to a refluxing solution of 3-bromoquinoline and isoamyl nitrite in chloroform for overnight, 3-bromo-1-(3',4'-dimethoxyphenyl)-2-trichloromethyl-1,2-dihydroquinoline **5e** was obtained in 45% yield (Scheme 5).

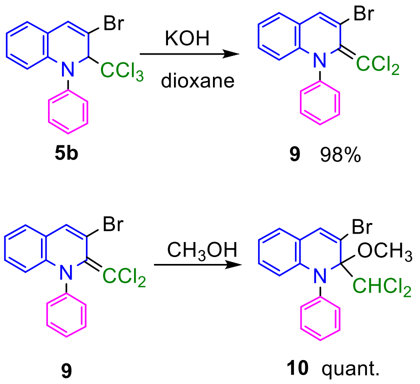


5e 45%

Scheme 5. Reaction of quinoline **4b** with benzyne prepared from anthranilic acid **1b** and chloroform

To further demonstrate the practical utilization of this newly developed methodology, multi-gram scale reaction of 3-bromoquinoline **4b** with anthranilic acid and isoamyl nitrite in chloroform by using 30 mmol of anthranilic acid, quinoline **4b** (15 mmol), and chloroform was performed, which resulted in the isolation of three-component product **5b** without any chromatographic separation in 74% (4.46 g, 11.1 mmol). Work-up process was simple; after finishing the reaction, the filtered solution was concentrated and added a small amount of methanol to give precipitated products. Separation of the precipitate afforded almost pure three-component product **5b**. Previous reports on the three-component reaction by using triflate were generally performed under 1 mmol scales.[3-4,6] The obtained products would not be applied to the starting materials for further reaction.

Since large scale synthesis of trichloromethylated quinoline **5b** was accomplished, the reaction of **5b** with base was tried. Hydrolysis by KOH in dioxane gave 2-(dichloromethylene)-1-phenyl-3-bromo-1,2-dihydro-quinoline **9** in almost quantitative yield. Treatment of **5b** with DBU in CH_2Cl_2 at rt or 24h gave the same product **9** in 95% yield. Reaction of **9** with methanol gave the corresponding adduct **10** in quantitative yield (Scheme 6). The structures of **9** and**10** were determined by spectroscopic analysis.



Scheme 6. Reaction of **5b** with KOH in dioxane

In conclusion, the first multi-component reaction of *in situ* formed benzyne with imines and pronucleophiles was successfully developed with the assistance of anthranilic acid as a starting benzyne precursor. *In situ* formed imines also reacted with benzyne to give the corresponding four-component products. Multi-gram scale synthesis was successfully accomplished and applied in the facile construction of 2-(dichloromethylene)-1-phenyl-1,2-dihydro-quinoline.

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