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Aryne Compatible Solvents are not Always Innocent

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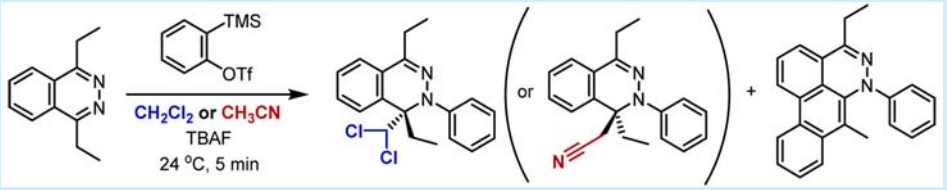
Supporting Information



ABSTRACT: Arynes are important and versatile intermediates in a variety of transformations. Commonly used solvents for aryne chemistry include acetonitrile and dichloromethane. Although rarely reported, the reactive nature of aryne intermediates makes them prone to side reactions, which sometimes involve solvent participation. Acetonitrile and dichloromethane are not always innocent solvents and can participate in aryne-based reactions. These results are presented in the context of ongoing mechanistic investigations of the triple aryne−tetrazine reaction.

Arynes have been utilized in a wide variety of transformations for the formation of multiple carbon−carbon, carbon−nitrogen, carbon−oxygen, and/or carbon−hydrogen bonds.[1−7] In comparison to an unstrained alkyne, arynes primarily exhibit high electrophilic reactivity due to LUMO lowering.[8] Several aryne-based reactions have been developed including σ-bond insertions,[9−12] nucleophilic additions,[13−15] ene reactions,[1,16−18] desaturations,[19] and cycloadditions, such as [4 + 2],[20−23] [3 + 2],[24−26] [2 + 2],[27,28] and [2 + 2 + 2][29−31] modes. Our laboratory is interested in new chemical tools and rapid access to new fluorescent probes.[32] Recently, we reported a new multistep aryne addition reaction referred to as the triple aryne−tetrazine (TAT) reaction.[32] The TAT reaction enables rapid access to a new class of polyaromatic heterocycles by coupling diverse reactivity modes between simple aryne and tetrazine[33] starting materials into a single multistep process (Figure 1). The TAT reaction provides a rapid route to several substituted dibenzo[*de*,*g*]cinnolines with unique fluorescent properties.

Aryne-based reactions are commonly performed in acetonitrile, dichloromethane, or combinations of both.[34−38] A few notable studies by Hoye[19,39] and Coe[40] have described solvent effects on aryne-based reactions. However, reports describing the reactivity of common solvents used in aryne chemistry are limited to tetrahydrofuran,[41,42] acetonitrile,[43] and other alkylnitriles.[44] During recent investigtions into the TAT reaction we found that dichloromethane, as well as acetonitrile, are not innocent solvents and can result in byproduct formation when deprotonated by the resulting intermediate aryl anion formed after an initial aryne addition reaction. We discovered that these common aryne compatible solvents can contribute to low yields by reacting with key intermediates along the TAT reaction pathway to produce solvent adducts. Herein, we describe the formation of these solvent adducts in the context of the TAT reaction, providing insight into the reactivity of commonly used organic solvents in aryne-based reactions.

During the course of the TAT reaction, a phthalazine is the first isolable intermediate, following an initial Diels−Alder/retro-Diels−Alder reaction of benzyne with a tetrazine. Benzyne precursor **2**[45] was used as the limiting reagent in a reaction with tetrazine **1** to prepare phthalazine intermediate **4** in 37% yield. Intermediate **4** was isolated and characterized (Scheme 1) prior to use as the starting material under the TAT

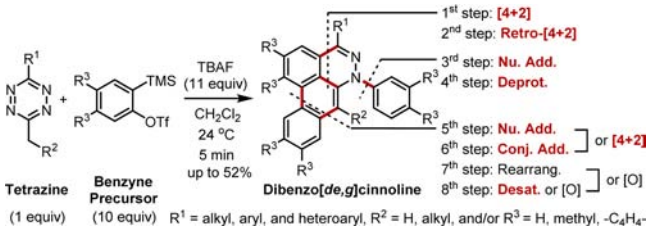
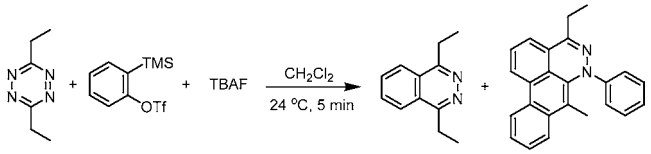


Figure 1. General scheme of the TAT reaction and proposed mechanistic steps. Red bold lines represent newly formed bonds. Red bold fonts denote aryne-engaged steps.

Scheme 1. Isolation of Phthalazine Intermediate 4



1	2		4	3
1 equiv	10 equiv	11 equiv	-	44%
2 equiv	1 equiv	1.1 equiv	37%	1%

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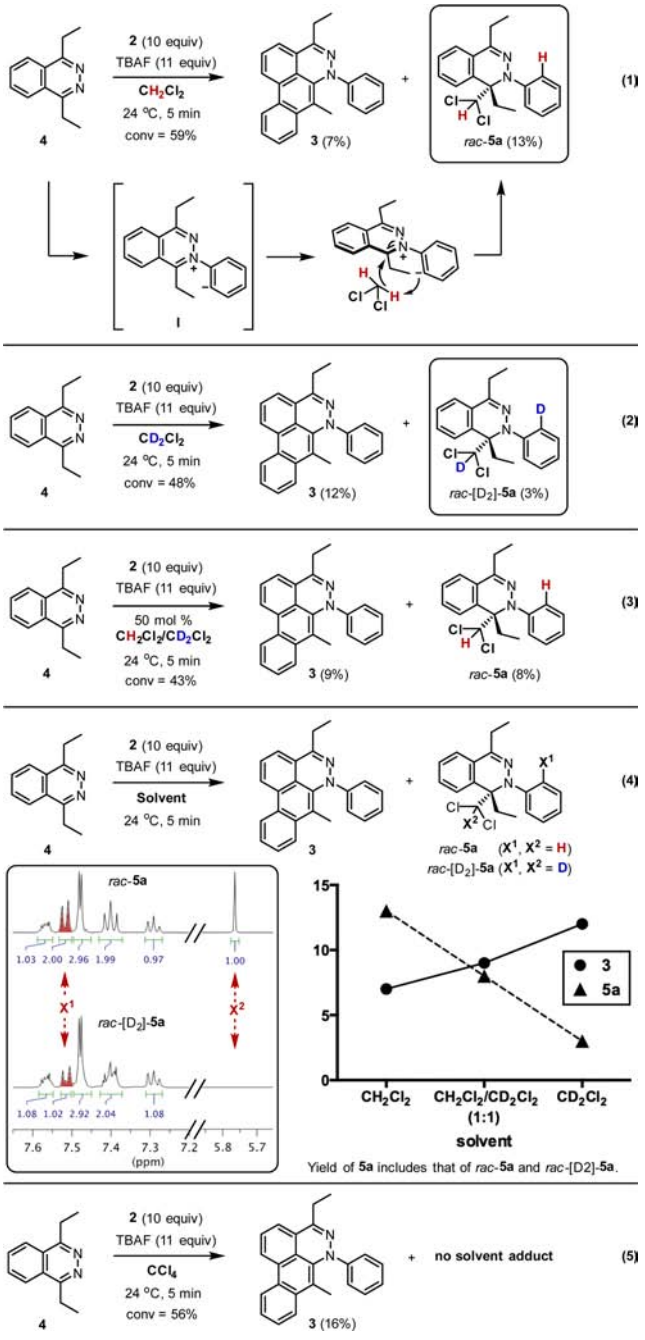
reaction conditions (Scheme 2, eq 1). Exposure of **4** to the TAT reaction conditions afforded desired product **3** in low

Scheme 2. Crossover Experiment for the Dichloromethane-Adduct Formation Reactions in CH_2Cl_2, CD_2Cl_2, 1:1 Mixture of CH_2Cl_2 and CD_2Cl_2, and CCl_4



yield (7%) (Scheme 2, eq 1), which is lower than the yield of **3** using the standard TAT reaction conditions (44%) (Scheme 1).[32] Interestingly, solvent adduct *rac*-**5a** was isolated from the complex reaction mixture (Scheme 2, eq 1). A trace amount of *rac*-**5a** was also observed in the standard TAT reaction. The crystal structure of **5a** (Figure 2) revealed that the dihydropyridazine ring is puckered with a dihedral angle (C1−N1−N2−C2 angle) of 28.2°. The N1−N2−C3−C4 dihedral angle between the dihydropyridazine plane and the

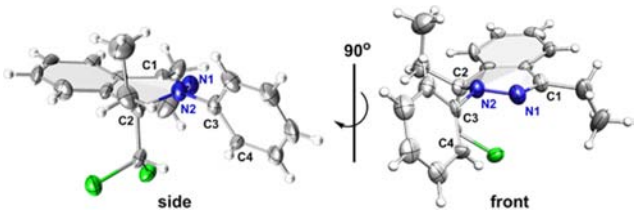


Figure 2. X-ray crystal structure of dichloromethane solvent adduct **5a**.

N-phenyl plane was 54.9° due to the sterics imposed by the adjacent fully substituted carbon center.

A plausible mechanism leading to the formation of *rac*-**5a** involves nucleophilic addition of phthalazine **4** to benzyne, producing nonisolable zwitterionic intermediate **I**. The resulting zwitterion then deprotonates dichloromethane, and the conjugate base attacks the hydrazonium species to afford solvent adduct *rac*-**5a**. To probe the reaction pathway from **4** to *rac*-**5a**, labeling experiments were performed using deuterated solvent. The reaction was conducted by addition of TBAF to **4b** and benzyne precursor **2**, using CD_2Cl_2 as the reaction solvent (Scheme 2, eq 2). The ^1H NMR analysis revealed a single deuterium (X^1 = D) on the *N*-phenyl group and a missing proton (X^2 = D) on the dichloromethyl substituent of *rac*-[D_2]-**5a**. The result supports the idea that the formation of the solvent adduct is indeed initiated by deprotonation by the aryl zwitterion **I**.

By varying the concentration of deuterated to nondeuterated solvent, a significant kinetic isotope effect (KIE) was observed in dichloromethane. The yield of *rac*-**5a** reached 13% in CH_2Cl_2 (Scheme 2, eq 1) and the reaction in CD_2Cl_2 afforded the corresponding product *rac*-[D_2]-**5a** in only 3% yield (Scheme 2, eq 2). Although the ratio of *rac*-**5a**:*rac*-[D2]-**5a** was 4:1, *rac*-[D_2]-**5a** was not observed when the reaction was conducted in a 1:1 mixture of CH_2Cl_2 and CD_2Cl_2 (Scheme 2, eq 3). As the amount of CD_2Cl_2 was increased, the yield of **3** increased and the yield of the solvent adduct (*rac*-**5a** or *rac*-[D_2]-**5a**) decreased (Scheme 2, eq 4). Solvents such as CH_2Cl_2 appear to be acidic enough to be deprotonated under the reaction conditions, and this leads to solvent adduct **5a**, as evidenced by the high KIE in CD_2Cl_2. Based on these results, we conducted the reaction in CCl_4 (Scheme 2, eq 5) and the yield of **3** was 16%, which was a higher yield of **3** than that obtained from the reaction in CH_2Cl_2, CD_2Cl_2, or a mixture of CH_2Cl_2/CD_2Cl_2 (Scheme 2, eq 4).

To determine if a solvent-trapped intermediate could be generated from other common organic solvents used in aryne chemistry, experiments were conducted in acetonitrile (Scheme 3, eq 6). This reaction afforded the acetonitrile adduct *rac*-**5b** in 8% yield. The zwitterion intermediate **I** also appears to be sufficiently basic enough to deprotonate acetonitrile. Note that the pK_a of benzene is 43 in H_2O,[46] and the pK_a of acetonitrile has been reported to be 31.3 in DMSO.[47] Similar to the dichloromethane solvent adduct **5a**, the X-ray crystal structure of **5b** exhibited a puckered conformation with a dihedral angle (C1−N1−N2−C2 angle) of 36.7° on the dihydropyridazine ring (Figure 3). Consistent with the structure of **5a**, the biaryl ring torsional angle (N1−N2−C3−C4) between the dihydropyridazine plane and the *N*-phenyl plane was found to be twisted 50.0° away from coplanarity.

To gain insight into the relative reactivity of the two different solvents with benzyne, crossover experiments were conducted on a 10 μmol scale with several different ratios of CH_2Cl_2 and

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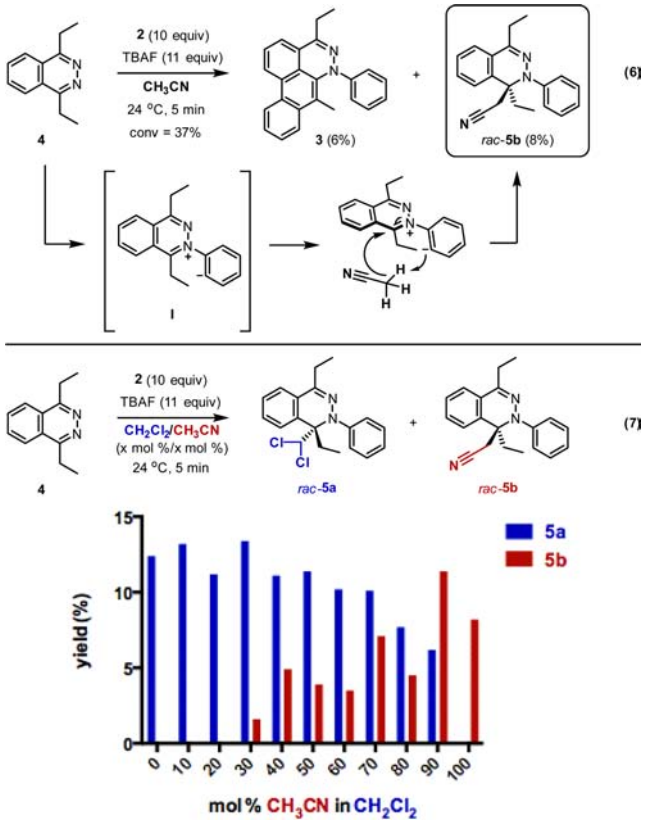
Scheme 3. Acetonitrile-Adduct Formation Reaction and Competitive Solvent Adduct Formation Using Different Ratios of CH_2Cl_2 and CH_3CN



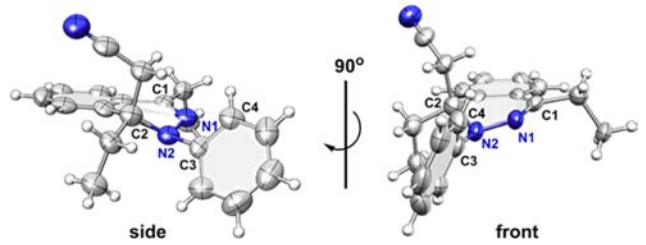
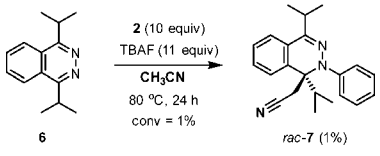


Figure 3. X-ray crystal structure of acetonitrile solvent adduct **5b**.

CH_3CN (Scheme 3, eq 7). Dichlromethane resulted in significant formation of the solvent adduct versus acetonitrile. When 1:1 CH_2Cl_2/CH_3CN was used as the solvent for the reaction, the yield of *rac*-**5a** was more than twice that of *rac*-**5b**.

To probe steric effects on solvent adduct formation, phthalazine **6** was subjected to the TAT reaction conditions in dichloromethane and acetonitrile at 24 °C. None of the possible solvent adducts were observed, and only starting material was recovered. Interestingly, when the reaction was conducted in acetonitrile at 80 °C for 24 h, the acetonitrile-adduct *rac*-**7** was produced in 1% yield (Scheme 4). This result

Scheme 4. Solvent Adduct *rac*-7 from Intermediate 6



indicates that the reaction is possible but strongly biased by the steric demands of the phthalazine substrate. The solvent adduct formation appears to be greatly influenced by the solvent pK_a and the substrate sterics.

Herein, we reported participation of dichloromethane and acetonitrile in aryne reactions with phthalazines. Isolation of dichloromethane and acetonitrile solvent adducts (*rac*-**5a** and *rac*-**5b**) demonstrates that common solvents thought to be compatible with aryne chemistry are not always innocent bystanders. Deuterium labeling experiments not only confirmed noninterrupted bimolecular reaction pathways between the zwitterionic intermediate **I** and dichloromethane, but also explained a solvent-engaged side reaction leading to lower yields of desired product **3** in the course of the TAT reaction. The crossover experiment of dichloromethane and acetonitrile highlighted that dichloromethane is more reactive than acetonitrile under TAT reaction conditions. As expected, the experiment with sterically bulky phthalazine **6** demonstrated that solvent adduct formation is affected by steric hindrance of the electrophile as well as pK_a. The discovery of solvent participation in TAT reaction side product formation provides insight into the reactivity of benzyne with two commonly used solvents. Similar side reactions may contribute to low yields in other aryne-based reactions. Additionally, these results could inspire new reactions for the construction of fully substituted carbon centers based on aryne addition/solvent capture reactions, as demonstrated in this report.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01977.

Experimental details and NMR spectra (PDF)
Crystallographic data for **5a** (CIF)
Crystallographic data for **5b** (CIF)

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Notes

The authors declare no competing financial interest.

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