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Controlled Reactivity of 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) in the Selective Synthesis of 1-(Bromoethynyl)arenes

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This work is dedicated to Dr. C. T. Rao (Sun Pharma Advanced Research Centre, Vadodara, India) on the occasion of his 58th birthday.

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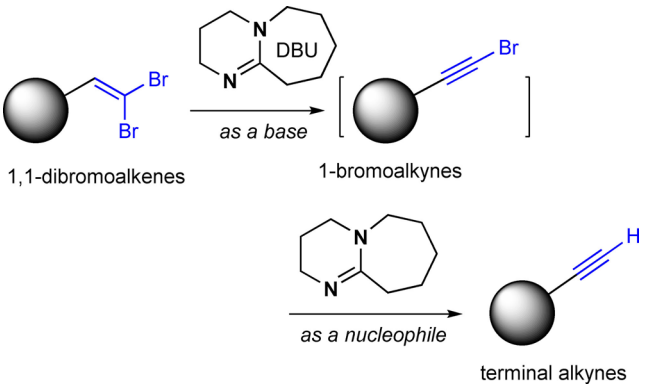
Abstract: The nucleophilic reactivity of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was completely controlled by the formation of monohydrate (DBU·H_2O) in the synthesis of 1-(bromoethynyl)arenes from 1,1-dibromoalkenes. Differential reactivity of DBU in protic solvents as compared to aprotic solvents has been explored to prevent the formation of mixtures of products in this reaction. Hydrated DBU is found to be superior to dry DBU, both for the selective synthesis and ease of isolation. In addition, use of DBU·H_2O as a non-nucleophilic mild base allowed us to synthesise 1-(bromoethynyl)-arenes *via* a reaction under solvent-free conditions. Utilization of DBU·H_2O as sole reagent also allowed us to isolate the products without column chromatographic purifications.

Keywords: alkynes; controlled reactivity; 1-bromoalkynes; 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU); 1,1-dibromoalkenes; non-nucleophilic bases

Introduction

Modification of a reagent is always a better way to achieve control of reactivity as compared to other methods like modification of substrate and/or modification of medium.[1] 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) is a reagent initially discovered as a non-nucleophilic base[2] and few years later the same compound was rediscovered for its nucleophilic character.[3] Recently, we have identified its dual role[4] (nucleophile and base) in the synthesis of terminal alkynes[5] from their corresponding 1,1-dibromoalkenes *via* the formation of intermediate 1-bromoalkynes[6] (Scheme 1).

As per the reactions presented in Scheme 1, it is important to control the nucleophilic character of the reagent DBU in order to isolate the 1-bromoalkyne in its pure form. In the present work, we describe a reagent-controlled selective synthesis method to access 1-bromoalkynes. It is well known that alkynes and 1-bromoalkynes are important starting materials in synthesis for the pharmaceutical, agricultural and polymer chemistry fields.[7] The 1-bromoalkynes are most applicable due to their relative stability and versatile reactivity with transition metal catalysts.[8] The presence of an alkyne functionality together with a bromine, leads to tunable electrophilic and nucleophilic properties, and sometimes can be used as dual role re-

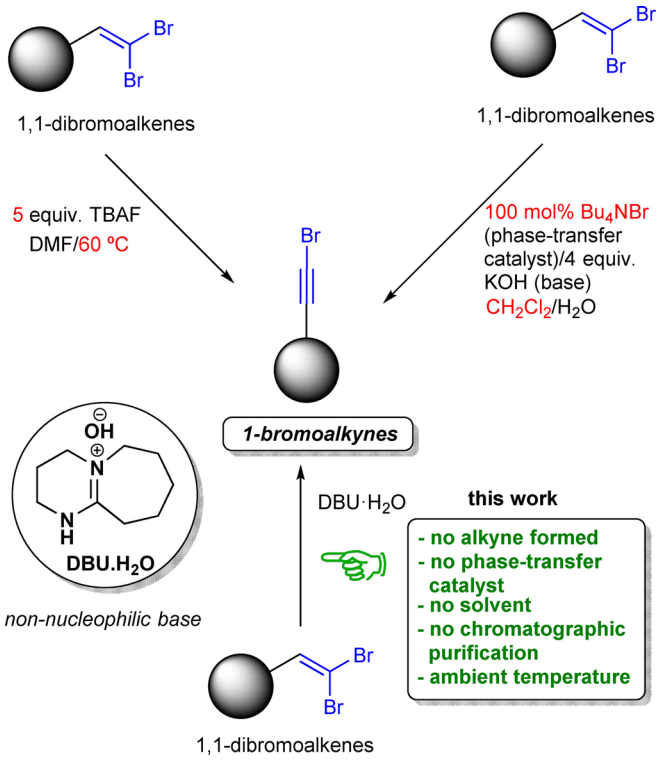


Scheme 1. Our work on the dual role of DBU in the synthesis of terminal alkynes.

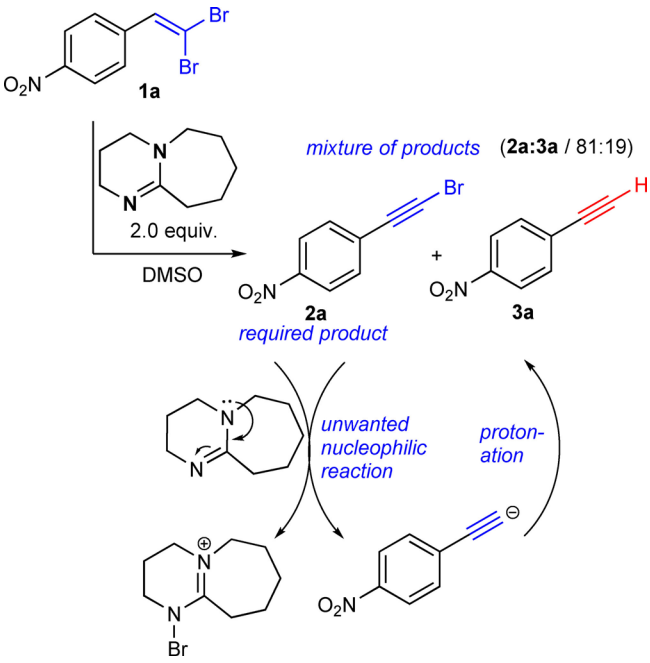
agent.[9] Owing to the emerging utility of the 1-bromoalkynes in synthetic organic chemistry and their usefulness as synthons in materials industry,[7,8m,n] there is a pressing need to develop practical and environmentally benign methods for their synthesis.

One of the popular methods for the synthesis of 1-bromoalkynes involves electrophilic bromination of terminal alkynes (or trimethylsilyl-substituted alkynes) with *N*-bromosuccinimide (NBS) and a metal salt such as $AgNO_3$.[10] The terminal alkynes in turn can easily be accessed from 1,1-dibromoalkenes by using the Corey–Fuchs reaction or its modified conditions.[4,11] Instead of terminal alkynes as precursors, researchers have also developed methods proceeding directly from 1,1-dibromoalkenes by the employment of strong bases such as DBU, LiHMDS, NaHMDS, etc.[12] In 2000, Lin et al. reported mild conditions with 100 mol% of tetrabutylammonium bromide (TBAB) and four equivalents of KOH in a biphasic dichloromethane/water solvent system (Scheme 2).[13] Recently, Mori et al. described the use of 5 equivalents of tetrabutylammonium fluoride (TBAF·3H_2O) in DMF at 60 °C (Scheme 2) for a similar transformation.[14]

The above methods suffer from the formation of mixtures of products or employment of toxic and pyrophoric reagents at cryogenic temperatures or utilization of metal salts or use of chlorinated solvents and employment of quantitative phase-transfer catalyst (or) utilization of excess of fluorinated reagents. Tedious column chromatographic purification is yet another drawback for all the prior mentioned methods. Although the report by Ratovelamanana et al.[12a] is very useful for the synthesis of 1-bromoalkynes containing electron-donating substituents using DBU base, the reaction of **1a** with DBU (Scheme 3) gave the corresponding 1-bromoalkyne **2a**, along with side product **3a** in an 81:19 ratio.[15] The formation of the undesired alkyne **3a** was in accordance with our previous observation[4] on the nucleophilic reaction of 1-bromoalkyne **2a** with DBU (Scheme 3).



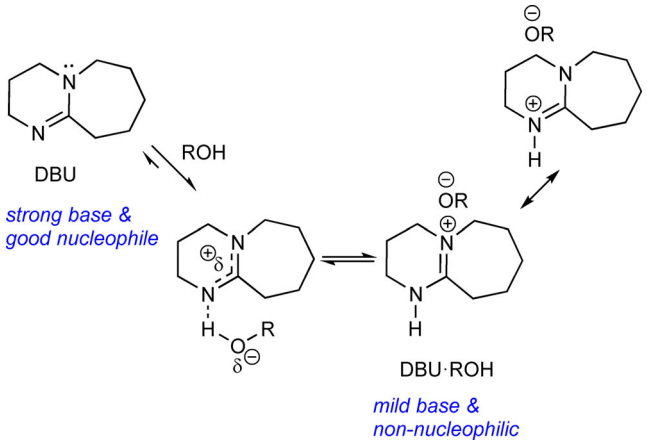
Scheme 2. Recent reports for the synthesis of 1-bromoalkynes.



Scheme 3. Rationale for the obtained mixture of products.

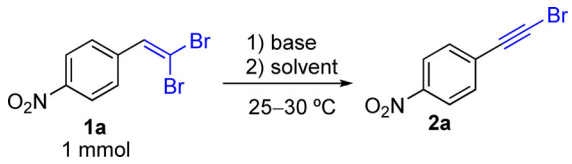
Based on the above observation, it was envisioned that controlling the nucleophilicity of DBU (Scheme 4) would be necessary in order to control the formation of unwanted **3a**. Since DBU is an excellent proton acceptor,[2] it was hypothesized that the good nucleophile DBU could be converted to a weak base with diminished nucleophilicity by conducting the reaction in protic solvents. As shown in Scheme 4, the nucleophilic nitrogen can be protonated or become engaged in hydrogen bonding, thus making it no longer available for nucleophilic reaction.

To realize our hypothesis we have initiated the elimination reaction on a challenging substrate, the electron deficient 1,1-dibromoalkene **1a** (Table 1) with DBU. In a preliminary experiment, performing the reaction of **1a** in the protic solvent MeOH, with 1 equivalent of DBU revealed a significant difference in the reactivity of DBU and gave the desired 1-bromoalkyne in 64% yield based on recovery of the start-



Scheme 4. Change in reactivity profile of DBU in protic solvents

Table 1. Optimization study.[a]



Entry	Base (equiv.)	Solvent (mL)	Time	Yield [%] of **2a**[b]
1	DBU (1)	MeOH (5)	48 h	64
2	DBU (2)	MeOH (5)	30 min	87
3	DBU (2)	EtOH (5)	30 min	86
4	DBU (2)	*t*-BuOH (5)	48 h	69
5	DBU (2)	H_2O (5)	30 min	30
6	DBU (2)	H_2O (5)	48 h	42
7	DBU (2)	H_2O (1)	12 h	70
8	DBU (2)	H_2O (0.1)	90 min	81
9	**DBU·H_2O (2)**	**–**	**25 min**	**94**
10	DBN·H_2O (2)	–	25 min	83
11	TMG·H_2O (2)	–	24 h	45
12	DBU·H_2O (1)	–	24 h	54
13	DBU·MeOH (2)	–	2 h	33

[a] *Reaction conditions:* **1a** (1.0 equiv., 1 mmol), base, and solvent at ambient temperature.
[b] Isolated yields. DBN = 1,5-diazabicyclo[4.3.0]non-5-ene, TMG = 1,1,3,3-tetramethylguanidine.

ing material (Table 1). Gratifyingly, no traces of alkyne **3a** were detected even after 2 days (Table 1, entry 1). This finding further confirmed our presumption that the protic solvent diminishes the nucleophilicity of DBU. Upon increasing the amount of DBU by one more equivalent in solvents like MeOH and EtOH, the reaction was complete in 30 min and afforded 1-bromoalkyne exclusively in very good yields (Table 1, entries 2 and 3). However, the reaction in *t*-BuOH was very sluggish (Table 1, entry 4).

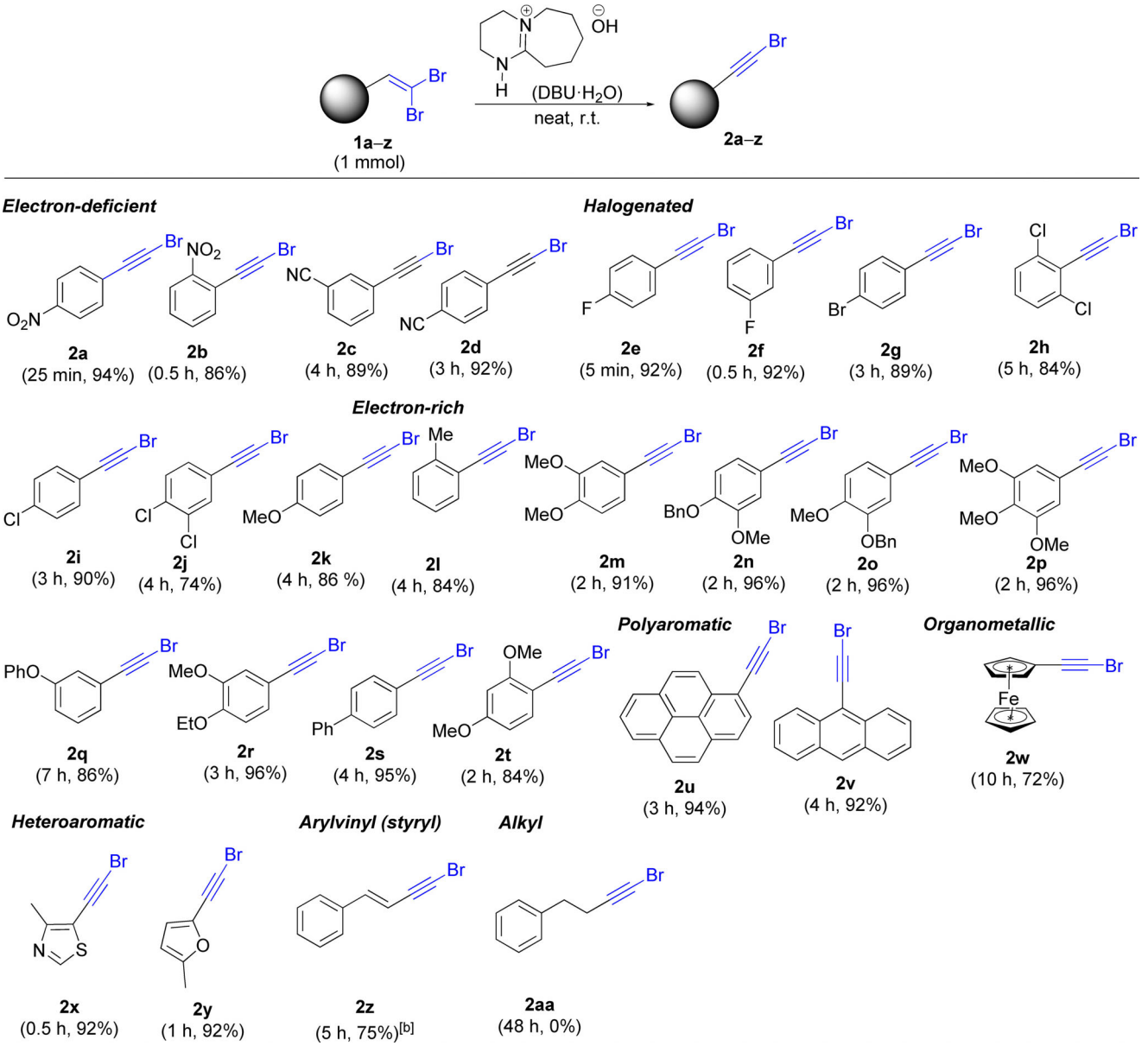
The above findings in protic solvents encouraged us to undertake the study in environmentally benign water as the solvent (Table 1, entries 5–8). Accordingly, use of about 0.1 mL mmol^{-1} of water was found to be the best in terms of yield and time (Table 1, entry 8). We have thereby observed "the increment in the rate of reaction with decrement in the amount of H_2O (entries 5–8)."

The above results intrigued us to test the reaction under solvent-free conditions (Table 1, entry 9) by utilizing freshly prepared DBU·H_2O.[16,17] To our delight, the reaction was found to be complete in 25 min and gave **2a** in excellent yield (Table 1, entry 9). However, the reactions of **1a** with DBN·H_2O or TMG·H_2O were found to proceed with lower yields (Table 1, entries 10 and 11). The starting material was not completely consumed with one equivalent of DBU·H_2O, while use of 2 equivalents of DBU·MeOH resulted in low yields of 1-bromoalkyne (Table 1, entries 12 and 13). Therefore, it was found that 2 equivalents of DBU·H_2O are essential for the complete consumption of starting material under solvent-free reaction conditions at ambient temperature. The product was isolated in its pure form without any chromatography, since the nitrogenous by-products generated in this reaction were soluble in aqueous acidic solution and were removed easily during the work-up. Alternatively, the product was easily isolated by the non-polar solvent (heptane) extraction from the reaction flask. The solvent used in the extraction was also recovered and reused.

Encouraged by the optimal reaction conditions (Table 1, entry 9), the scope and generality of this protocol for the synthesis of several 1-bromoalkynes **2a–z** from 1,1-dibromoalkenes **1a–z** were investigated (Table 2). As shown in Table 2, various 1-bromoethynylarenes bearing electron-withdrawing groups **2a–f**, halogens **2e–j** and electron-donating groups **2k–t** on the benzene ring were synthesized using this reaction with high efficiency.

However, the electronic properties of the substituents had shown obvious effects on the reaction rates (Table 2). A decreased reaction rate was observed in the case of substrates having electron-donating groups compared to those with electron-deficient groups. The steric hindrance on the benzene ring was very well tolerated in the case of *ortho*-substituted substrates that afforded 1-bromoalkynes such as **2b**, **2h**, **2l** and **2t**. Furthermore, polyaromatic 1-bromoalkynes **2u** and **2v** were also obtained using this protocol with excellent yields. Notably, nitrogen-, sulfur- and oxygen-containing heteroaromatic compounds, **2x** and **2y**, also were synthesized in good yields under the above solvent-free conditions. The ability to synthesize organometallic compound **2w** and α,β-unsaturated (styryl-substituted) 1-bromoalkyne **2z** demonstrates another advantage for this protocol, such compounds with sensitive functionalities would not survive under strong basic conditions. In contrast, the alkyl-substi-

Table 2. Substrate scope.[a]



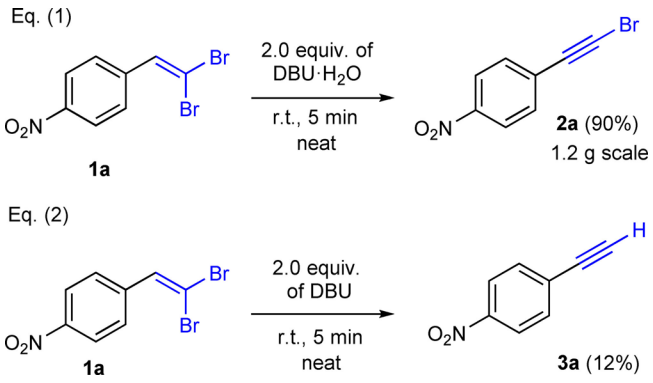
[a] *Reaction conditions:* **1** (1.0 equiv., 1 mmol), DBU·H_2O (2 mmol) at ambient temperature. Reaction time and isolated yield are given in parenthesis.
[b] Yield calculated as an average of two batches.

tuted 1-bromoalkyne **2aa** was not observed under the above reaction conditions, the complete recovery of the starting material further highlights the selective reactivity of DBU·H_2O in such transformations.

The synthesis of the representative electron-poor 1-bromoalkyne **2a** [Eq. (1), Scheme 5] was demonstrated on a gram scale under optimized reaction conditions, further confirming the efficiency and robustness of the present protocol. In contrast, an exothermic reaction was observed when 1,1-dibromoalkene **1a** was treated with dry DBU in solvent-free conditions and the corresponding terminal alkyne **3a** (12%) was obtained with no trace of the1-bromoalkyne [Eq. (2), Scheme 5].

Conclusions

In conclusion, the differential reactivity of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in protic solvents as compared with aprotic solvents has been explored to control its nucleophilicity. We have devised an efficient method for the selective synthesis of 1-(bromoethynyl)arenes using hydrated DBU (DBU·H_2O) at



Scheme 5. Scale-up synthesis of 1-bromoalkyne **2a** and solvent-free reaction of **1a** with dry DBU.

ambient temperature. The unique characteristics of DBU·H_2O tolerated an assortment of substrates and gave excellent yields under solvent-free conditions. Thus the method developed in the present study might find immense utility as a replacement for the conventional reagents.

Experimental Section

General Procedure for the Synthesis of 1-Bromoalkynes 2

To a 5-mL screw-cap vial containing dibromoalkene **1a–z** (1 mmol) was added freshly prepared DBU·H_2O (0.334 mL, 2.0 mmol, 2 equiv) dropwise over a period of 1 min against the walls of vial at ambient temperature (25–30 °C). The reaction mixture was allowed to stir at ambient temperature for the given time. After completion of reaction (monitored by TLC), the reaction mixture was quenched by addition of water (10 mL) and the resulting mixture was extracted with EtOAc/hexane (1:1, 2×10 mL); the organic layers were washed with 5 N aqueous HCl (10 mL) and water (10 mL). The organic layers were dried over anhydrous $MgSO_4$, the solvent was evaporated under reduced pressure, and resulting residues were dried under high vacuum to afford the corresponding analytically pure 1-bromoalkynes **2a–z**.

Alternative General Procedure for Product Isolation

Upon completion of the reaction, the product was extracted in heptane (3×10 mL) and washed with 5 N HCl (5 mL). The combined heptane layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulted residues were dried under high vacuum to afford the corresponding analytically pure 1-bromoalkynes **2a–z**. Heptane was recovered from the concentration and reused for the extraction of another experiment.

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