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One pot synthesis of 4,5-dibromo-3,6-diarylpyridazine from 1,4-diarylbuta-1,3-diyne

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A one-pot two-step methodology has been developed for the synthesis of 4,5-dibromo-3,6-diarylpyridazines starting from easily available starting material 1,4-diarylbuta-1,3-diynes. The reaction goes through the electrophilic addition of Br^+ ion with alkyne bonds followed by nucleophilic addition of hydrazine and intramolecular cyclization.

Keywords: Diyne, NBS, Cyclization, One pot reaction, Pyridazine

Pyridazine is an important class of aromatic heterocyclic compounds having two nitrogens in its ring and hence it belongs to the diazine family.[1] Natural sources of pyridazines are rare although it is an important scaffold present in many pharmacophores.[2] Pyridazine ring is chosen as a promising unit for drug design due to some attractive physicochemical features of a drug molecule present within it. For example, minaprine[3] acts as an antidepressant drug while pildralazine and hydralazine are used for the treatment of hypertension.[4] 3-Amino- 6-arylpyridazine is used as a selective CB2 agonist (Fig. 1).[5] The pyridazine based drug molecule has also been employed as a good inhibitor to the central nervous system (CNS) disorders.[6] Pyridazine derivatives also exhibit fungicidal and antibacterial activities and thus are applied as agrochemicals.[7] Pyridazine scaffold are also found in few liquid crystal compounds (Fig. 1).[8] Because of the applications in various fields, pyridazine derivatives are of much importance in academia as well as in pharmaceutical industry. Hence, various procedures have been developed for the synthesis of pyridazine derivatives.[9,10]

However, most of them involved the condensation between a 1,4-diketone with hydrazine followed by oxidation for aromatization.[9] As the synthesis of suitably designed starting 1,4-diketone derivative involves a number of steps, thus the final product formation involves multiple steps. Herein, we have developed a one-pot reaction methodology for the synthesis of 3,4,5,6-tetra substituted pyridazine starting from our previously synthesized linear 1,4-diarylbuta-2,3-diynes.[11]

Experimental Details

General method

High quality reagents were purchased from Sigma Aldrich. Analytical grade commercial reagents and solvents were purified by standard procedures prior to use. Chromatographic purification was done with 60-120 mesh silica gel (Merck). For reaction monitoring, pre-coated silica gel 60 F254 sheets (Merck) were used. NMR spectra were recorded on a BRUCKER-AC 400 MHz spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (deuterochloroform: 7.26 ppm). Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), coupling constant (Hz).

General reaction procedure for the synthesis of 1,4-diarylbuta-1,3-diyne[11]

$PdCl_2$ (5 mol%), Na_2CO_3 (1 equiv.) and TBAB (1 equiv.) were taken in a two neck round bottomed flask and then 2.5 mL water and 0.5 mL EtOAc were added to it. Then 0.5 mmol of aryl acetylene was added to the reaction vessel and stirred at room temperature with continuous air bubbling through a syringe. After completion of the reaction, the reaction mixture was extracted with ethyl acetate (20 mL × 3). Then combined organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated

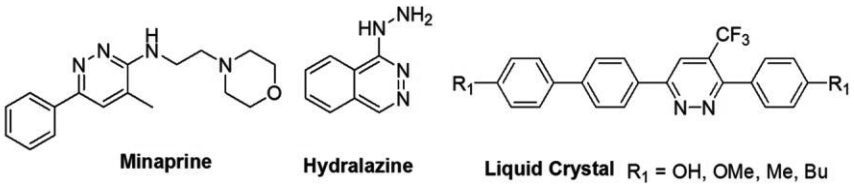


Fig. 1 — Structures of molecules containing pyridazine ring

at reduced pressure. Finally, the crude product was purified by column chromatography using silica gel (60–120 mesh) as stationary phase and 2% ethyl acetate in hexane as the eluent.

Typical reaction procedure for the synthesis of 4,5-dibromo-3,6-diaryl pyridazine

The substrate 1,4-diphenylbuta-1,3-diyne (0.5 mmol), N-bromosuccinamide (1.5 mmol) and 3mL of solvent mixture acetonitrile-water (10:1) were taken in a round bottomed flask and then heated at 50°C for 30 min. Then hydrazine hydrate (1 mmol) was added and the reaction was continued for another 3 h. After completion, the reaction mixture was cooled to room temperature and then saturated sodium thiosulphate solution was added to decompose excess bromine. The reaction mixture was extracted with ethyl acetate solution (3 x 20 mL) and the combined organic layer was washed with brine and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure and the crude product was purified in column chromatography using EtOAc-Hexane (10:1) mixture.

Analytical data

4,5-Dibromo-3,6-diphenyl pyridazine (2a): Yellow solid, m. p.: 100-101°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.52-7.54 (6H, m), 7.73-7.80 (4H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 128.4 (4 x CH), 129.8 (4 x CH), 129.9 (2 X CH), 132.0 (2 X C), 137.0 (2 X C), 161.0 (2 X C). Analytical data required for $C_{16}H_{10}Br_2N_2$: C, 49.27; H, 2.58; N, 7.18. Found: C, 49.25; H, 2.56, N, 7.20.

4,5-Dibromo-3,6-bis(4-methylphenyl) pyridazine (2b): Yellow solid, m. p.: 105-106°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.46 (6H, s), 7.33 (4H, d, *J* = 8.0 Hz), 7.65 (4H, d, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 21.6 (2 x CH_3), 129.0 (4 x CH), 129.7 (4 x CH), 131.8 (2C), 134.4 (2C), 140.1 (2C), 160.8 (2C). Analytical data required for $C_{18}H_{14}Br_2N_2$: C, 51.71; H, 3.37; N, 6.70. Found: C, 51.73; H, 3.35; N, 6.71.

4,5-Dibromo-3,6-bis(3-methylphenyl) pyridazine (2c): Yellow solid, m. p.: 104-105°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.46 (6H, s), 7.33 (2H, d, *J* = 7.6 Hz), 7.42 (2H, t, *J* = 7.6 Hz), 7.52-7.55 (4H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 21.6 (2 x CH_3), 126.8 (2 X CH), 128.2 (2 X CH), 130.3 (2 X CH), 130.61 (2 X CH), 131.9 (2C), 137.0 (3C), 138.1 (2C), 161.1 (2C). Analytical data required for $C_{18}H_{14}Br_2N_2$: C, 51.71; H, 3.37; N, 6.70. Found: C, 51.70; H, 3.35; N, 6.69.

4,5-Dibromo-3,6-bis(4-methoxyphenyl) pyridazine (2d): Yellow solid, m. p. 173-174°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.90 (6H, s), 7.04 (4H, d, *J* = 8.6 Hz), 7.74 (4H, d, *J* = 8.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 55.6 (2 x CH_3), 113.8 (4 x CH + 2XC), 131.5 (4 X CH), 160.1 (2 X C), 161.1 (2 XC). Analytical data required for $C_{18}H_{14}Br_2N_2O_2$: C, 48.03; H, 3.13; N, 6.22. Found: C, 48.00; H, 3.12; N, 6.24.

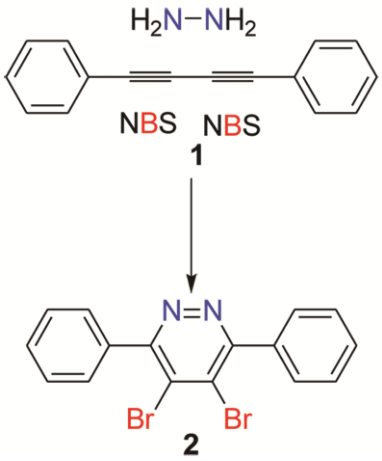
4,5-Dibromo-3,6-bis(3-fluorophenyl) pyridazine (2e): Yellow solid, m. p.: 134-135°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.22-7.24 (2H, m), 7.39-7.59 (6H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 117.0 (2 x CH, d, *J* = 11 Hz), 117.2 (2 x CH, d, *J* = 7 Hz), 125.6 (2 x CH, d, *J* = 3 Hz), 130.1 (2 x CH, d, *J* = 9 Hz), 132.0 (2 x C), 138.8 (2 x C, d, *J* = 8 Hz), 160.1 (2 x C), 162.5 (2 x C, d, *J* = 246 Hz). Analytical data required for $C_{16}H_8Br_2F_2N_2$: C, 45.11; H, 1.89; N, 6.58. Found: C, 45.14; H, 1.91; N, 6.59.

4,5-Dibromo-3,6-bis(3-chlorophenyl) pyridazine (2f): Yellow solid, m. p.: 172-173 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.45-7.52 (4H, m), 7.62 (2H, d, *J* = 7.2 Hz), 7.73 (2H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 127.9 (2 x CH), 129.7 (2 x CH), 129.9 (2 x CH), 130.2 (2 x CH), 132.0 (2 x C), 134.4 (2 x C), 138.4 (2 x C), 160.1 (2 x C). Analytical data required for $C_{16}H_8Br_2Cl_2N_2$: C, 41.87; H, 1.76; N, 6.10. Found: C, 41.86; H, 1.75; N, 6.07.

4,5-Dibromo-3,6-bis(4-fluorophenyl) pyridazine (2g): Yellow solid, m. p.: 167-168°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.20-7.24 (4H, m), 7.73-7.77 (4H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 115.6 (4 x CH, d, *J* = 21 Hz), 131.9 (4 CH, d, *J* = 8 Hz), 133.0 (2 x C, d, *J* = 3 Hz), 160.1 (C), 162.6 (C), 165.1 (C). Analytical data required for $C_{16}H_8Br_2F_2N_2$: C, 45.11; H, 1.89; N, 6.58. Found: C, 45.08; H, 1.88; N, 6.60.

Results and Discussion

Initially we have anticipated that if we are able to have a reaction of 1,3-diyne with two equivalents of N-bromosuccinimide (NBS) as the electrophilic reagent (E^+) and hydrazine as the dinucleophilic reagent then a cyclization product pyridazine may be obtained in a single-step reaction (Scheme 1). To test our proposition, we have performed a reaction of the 1,4-diphenyl-1,3-diyne, NBS and hydrazine. At first, the diyne was reacted with NBS (2 equiv.) and hydrazine hydrate (1 equiv.) in dichloromethane solvent at room temperature and we got about 13% of the product 4,5-dibromo-3,6-diphenylpyridazine. After confirming the structure, we have examined



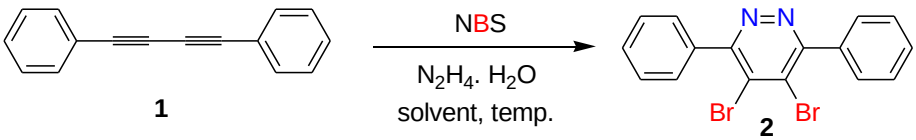
Scheme 1 — Anticipation for the synthesis of tetrasubstituted pyridazine

other conditions to improve the reaction yield. In varying different solvents, we found that the yield was little improved (22%) in acetonitrile and no product was isolated in case of water as the solvent. ^{1}H and ^{13}C NMR spectra of all the products are available in the Supplementary Information.

Then we increased the amount of NBS and hydrazine (Table 1, entry 6) and found that the yield was slightly improved. Then we changed the reaction strategy to a one-pot two-step process. At first, the reaction was performed the diyne and NBS for 30 min and then hydrazine hydrate was added. A sharp improvement of yield with this sequence was observed (entry 7). This is probably occurring because the Br^+ ions coordinated with the alkyne bonds and then nucleophile attack occurs.

The yield was further improved when we used acetonitrile along with a little amount of water (10:1). When we changed the ratio of acetonitrile and water to 2:1, then yield was decreased to 40%. This is probably because a small amount of water favours the solubility of succinamide salt but an excess amount of water disfavours the condensation with hydrazine. The product formation was increased with the increase of the reaction temperature to 50°C (Table 1, entry 11). All the screening results are shown in Table 1 and we found that the highest yield was obtained when the dyine was reacted with 3 (equiv.) of NBS in the acetonitrile-water solvent mixture (10:1) at 50°C.

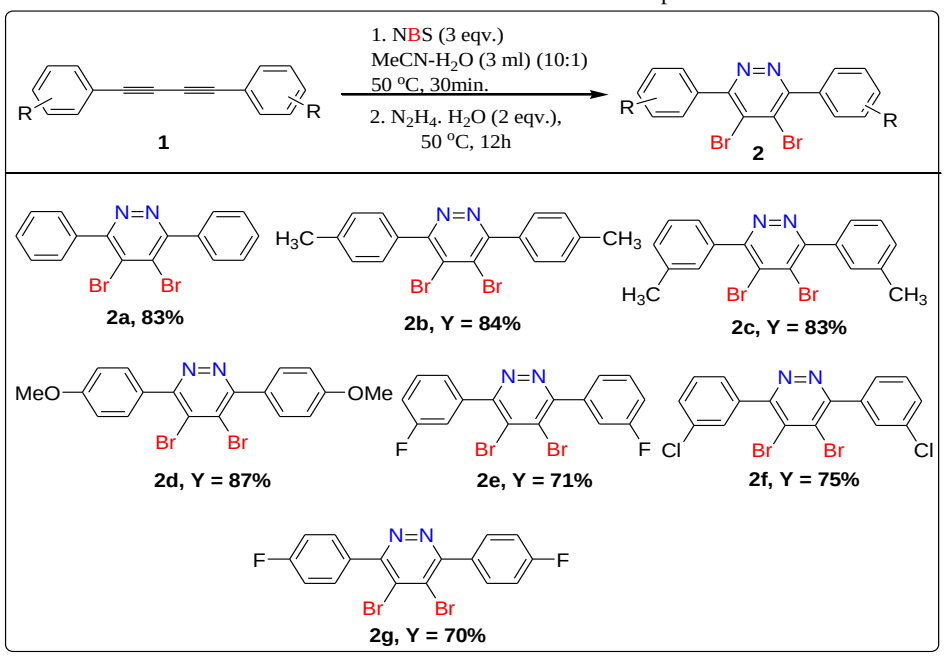
Table 1 — Screening of the reaction conditions



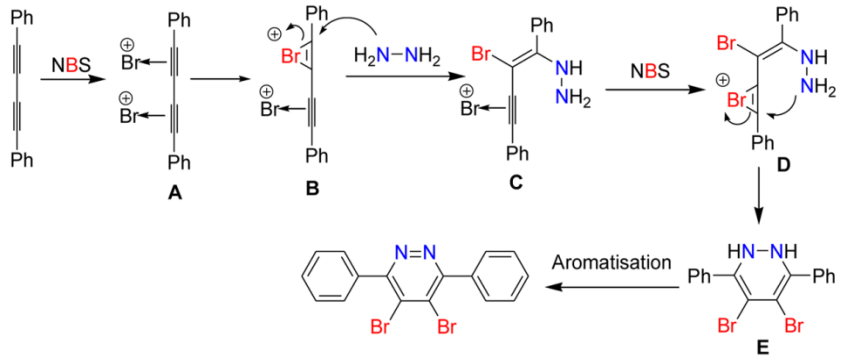
Entry[a]	Solvent	NBS (eqv.)	N_2H_4 (eqv)	Time (h)	Temp. (°C)	Yield (%)[b]
1	DCM	2	1	24	r.t.	13
2	DCE	2	1	24	r.t.	14
3	MeCN	2	1	24	r.t.	22
4	DMF	2	1	24	r.t.	Trace
5	H_2O	2	1	24	r.t.	00
6	MeCN	3	2	24	r.t.	27
7*	MeCN	3	2	24	r.t.	53
8*	MeCN+H_2O (10:1)	3	2	12	r.t.	65
9*	MeCN+H_2O (2:1)	3	2	12	r.t.	40
10*	MeCN+H_2O (10:1)	4	2	12	r.t.	60
11*	MeCN+H_2O (10:1)	3	2	3	50	83
12*	MeCN+H_2O (10:1)	3	2	3	70	83

*Condition-1: Reactions were performed with 0.5 mmol of 1,4-diphenylbuta-1,3-diyne, NBS and hydrazine hydrate in 3 mL solvent at room temperature. Condition-2:*Reactions were performed with 0.5 mmol of 1,4-diphenylbuta-1,3-diyne, NBS in 3 mL MeCN-H_2O (10:1) for 30 min and then hydrazine hydrate was added.* [b]*Isolated yield.*

Table 2 — Examination of the substrate scope [a,b]



[a]*Reactions were performed with 0.5 mmol of 1,4-diphenylbuta-1,3-diyne, NBS and hydrazine hydrate in 3 ml solvent at room temperature.* [b]*Isolated yield.*



Scheme 2 — Probable reaction mechanism

After getting the optimized reaction conditions, we wished to apply it on various substituted 1,3-diynes to examine the reaction scope. We have examined seven different substituted 1,3-diaryl-buta-1,4-diyne derivatives and observed that electron rich-substrate gave higher yield (Table 2, Entry 2d) and the electron-deficient substrates gave lower yield (Entry 2e-2g). These low yields are probably because of the lower reactivity of the electrophile (Br^+) with alkyne. However, the overall yields of the products were moderate to good. The NMR data are given in the SI.

Reaction mechanism

A plausible reaction mechanism for the formation of the products is shown in Scheme 2. At first NBS releases Br^+ which coordinates with the alkyne bonds (**A**). Then it converted to cyclobromonium ion where the nucleophilic attack occurs (**B**). A similar nucleophilic attack occurs to another triple bond to form the cyclized dihydro pyridazine (**E**) which then undergoes aromatisation to form the long conjugated stabilized product 3,6-diphenyl-4,5-dibromopyridazine.

Conclusion

We have developed an efficient one-pot methodology for the synthesis of 3,4,5,6-tetrasubstituted pyridazine starting from linear 1,4-diarylbuta-1,3-diyne. Our reaction methodology is simple, easy to handle, under open air conditions with commercially available cheap starting materials.

The developed procedure is short and easy to handle at normal laboratory conditions and the dibromopyridazine product could be used as a scaffold for further functionalization using cross-coupling reactions.

Supplementary Information

Supplementary information is available in the website http://nopr.niscpr.res.in/handle/123456789/58776.

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