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DMSO–allyl bromide: a mild and efficient reagent for atom economic one-pot *N*-allylation and bromination of 2°-aryl amines, 2-aryl aminoamides, indoles and 7-aza indoles†

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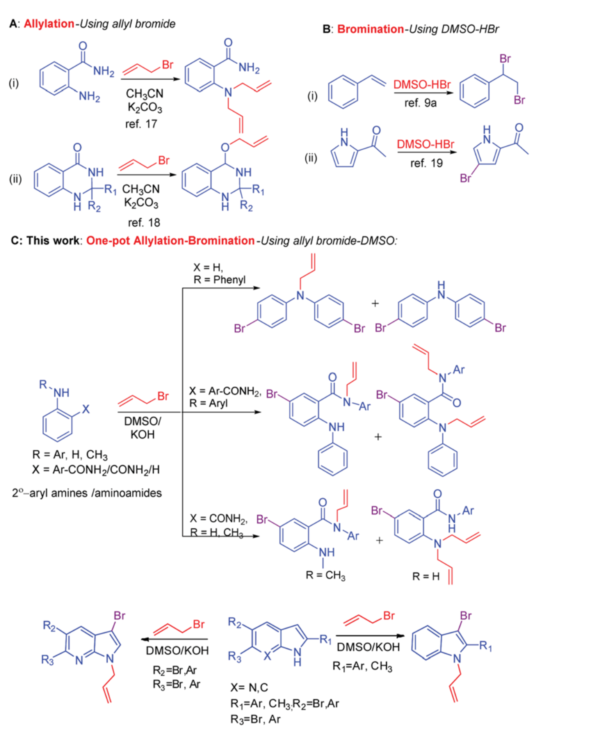
A mixture DMSO–allyl bromide has been developed as a reagent for an atom economic one-pot *N*-allylation and aryl bromination under basic conditions. Utilizing this reagent, *N*-allylation–bromination of a number of 2°-aryl amines, aryl aminoamides, indoles, and 7-aza indoles has been achieved. The scope of the substrates and limitations, the synthetic utility of the products, and a plausible reaction mechanism have been proposed.

Bromination of aromatic compounds is an important transformation in organic synthesis.[1] Aryl bromides are versatile synthons for functionalized aromatic compounds.[2] Thus, a number of reagents have been developed for the bromination reaction include electrophilic substitution using molecular bromine,[1,2] a dioxane–bromine complex for the direct bromination of aromatic amines,[3] NBS,[4] $CuBr_2$,[5] $LiBr/O_2$,[6] KBr/oxone,[7] and NH_4Br/H_2O_2.[8] Nevertheless, the use of molecular bromine requires harsh conditions and is associated with hazardous waste and polybromination.[1,2] In addition, the combination of the DMSO–aq. HBr system generates bromodimethyl sulfonium bromide (BDMS) species *in situ*,[9] and acts as a versatile brominating reagent for olefins, alkynes, ketones and α-bromination of β-ketoesters.[10,11] In addition to bromination, BDMS also catalyzes Mannich type reaction,[12] dethiacetalization of thioacetals to carbonyls,[13] oxidative coupling of thiols to disulfides,[14] ring-opening of epoxides and aziridines,[15] conversion of benzyl amines to benzoic acids *via* diazotization,[16] oxidation of indoles to oxindoles[17] and oxidative bromination and iodination of arenes and heteroarenes using DMSO–HX.[18] Allyl bromide is a versatile reagent used for *N*- or *O*-allylation of aromatic amines[19] and phenols.[20] Recently, we have reported a microwave-assisted *N*-allylation of anthranilamide,[21] and M. Guo *et al.*,[22] reported the *O*-allylation of quinazolinone using allyl bromide/base (Scheme 1A). Primarily, the combination of DMSO–HBr system is well known for the bromination of olefins[10a] and electrophilic bromination of aromatic compounds[23] (Scheme 1B). One-pot synthesis is a well-known method to



Scheme 1 Literature reports on (A) allylation (B) bromination and (C) present work.

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† Electronic supplementary information (ESI) available: Detailed experimental procedure, characterization data and copies of all the spectra of all the new compounds have been provided. Crystallographic information of compounds **3c** and **3l** is provided. CCDC 2101632 and 2045826. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1ra08588c

Scheme 2 Synthesis of compounds **3a** and **4a**.

conduct sequential multiple reactions in one reaction vessel[24] and has advantages over the multistep synthesis in terms of atom economy,[25] step economy,[26] redox economy, thus reducing the number of steps.[27] Minimization of waste production or loss of molecules without including in the products during a chemical reaction[28] is necessary atom economy protocol,[29] for example, the Diels–Alder reaction is an ideal chemical reaction in terms of atom economy and selectivities.[30] Hence, utilization of one-pot atom economic reaction is of current interest of organic synthesis.

During a synthesis in one of our current projects, when the combination of DMSO–allyl bromide under basic condition has been used for allylation of a secondary aryl amide, an unforeseen atom economic one-pot *N*-allylation–bromination reaction has been observed. To the best of our knowledge, the combination of DMSO–allyl bromide reagent system has never been used as a dual source of one-pot allylation and bromination reactions. The serendipity observation emerges the DMSO–allyl bromides system as a reagent for atom economic one-pot *N*-allylation and bromination of 2°-aryl amines and other substrates include 2-aryl amino amides,[31] indoles, and 7-aza indoles. The details are reported in this manuscript (Scheme 1C).

Initially, a reaction of diphenylamine **1a**, allyl bromide **2a** in DMSO (3 mL) and KOH at RT was investigated. The reaction provided the unexpected one-pot allylation–bromination product **3a** along with dibrominated compound **4a** in 50%, and 10% yields, respectively and found that the mixture of allyl bromide–DMSO/KOH emerged as a reagent system (Scheme 2, Table 1, entry 1). The *N*-allylated product **5a** was not formed. The formation of both products **3a** and **4a** was confirmed from spectroscopic analysis (see ESI†).

To explore the optimum condition, reaction parameters such as temperature, time, base and equivalence of alkyl halide **2a** and solvent were considered (Table 1). Besides, to speed up the reaction, under microwave (MW) irradiation, a mixture of 1 equiv. of diphenylamine **1a** and 2.2 equiv. of allyl bromide **2a**, and KOH in DMSO was MW irradiated for 5 min at 100 W, and no desired product was obtained (Table 1, entry 2). However, the reaction upon heating at 70 °C for 6 h afforded products **3a**, and **4a** in 50% and 15% yields, respectively (Table 1, entry 3). Extending the reaction time to 12 h and 24 h slightly improved the yields (Table 1, entries 4 & 7). To find out whether initially allylation or bromination takes place, repeating the above experiment for one hour afforded only allylated product **5a** while another reaction stopped at 4 h afforded three products **5a**, **3a**, and **4a** in 40%, 35%, and 8% yields respectively (Table 1, entries 5 & 6). This indicates initially allylation took place followed by bromination occurring *via* active species BDMS to yield the final product. Further, bases such as NaH and *t*-BuOK

Table 1 Optimization of synthesis of compounds **3a** and **4a**

Entry[a]	2a (equiv.)	Condition	Product(s) (% yield)[b] 5a	3a	4a
1	**2a** (2)	DMSO/KOH, RT, 72 h	—	50	10
2	**2a** (2)	DMSO/KOH, MW, 5 min	—[c]	—	—
3	**2a** (2)	DMSO/KOH, 70 °C, 6 h	—	50	15
4	**2a** (2)	DMSO/KOH, 70 °C, 12 h	[d]	71	16
5	**2a** (2)	DMSO/KOH, 70 °C, 1 h	90	—	—
6	**2a** (2)	DMSO/KOH, 70 °C, 4 h	40[d]	35	8
7	**2a** (2)	DMSO/KOH, 70 °C, 24 h	—	70	20
8	**2a** (2)	DMSO/NaH, 70 °C, 12 h	—	60	15
9	**2a** (2)	DMSO/KO^{t}Bu, 70 °C, 12 h	—	65	15
10	**2a** (4)	DMSO/KOH, 70 °C, 12 h	—	56	10
11	**2a** (2)	DMSO/KOH, 70 °C, 12 h[e]	—	30	60
12	$CuBr_2$	DMSO/KOH, 70 °C, 12 h[e]	—	—	10
13	**2a** (2)	DMSO/KOH, 70 °C, 24 h[e]	—	30	60
14	**2a** (2)	Dioxane/KOH, 70 °C, 12 h	80	—	—
15	**2a** (2)	CH_3CN/KOH, 70 °C, 12 h	85	—	—
16	**2a** (2)	2.5 equiv. DMSO, dioxane, KOH, 70 °C, 12 h		52	14
17	**2a** (2)	2.5 equiv. DMSO, CH_3CN, KOH, 70 °C, 12 h		50	15

[a] Substrate **1a** was used from entries 1–17. [b] Isolated yield. [c] MW irradiation is not suitable. [d] Optimized condition. [e] 2.5 equiv. of $CuBr_2$ was added as additive.

Table 2 Scope of the reaction

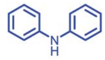
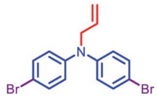
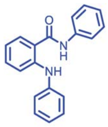
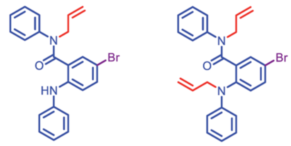
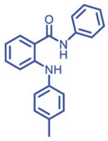
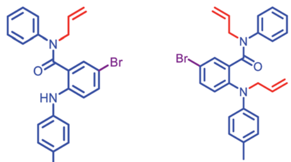
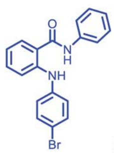
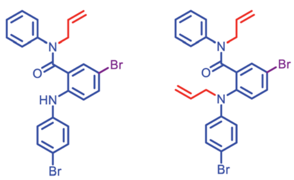
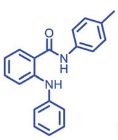
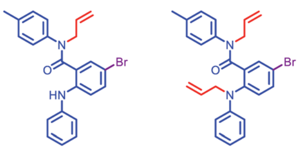
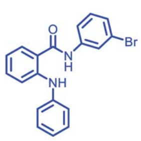
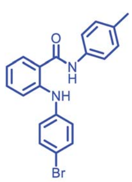
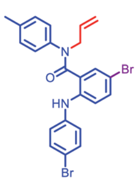
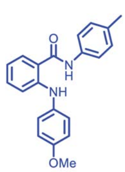
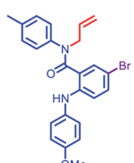
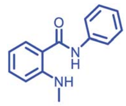
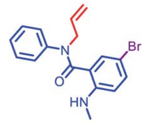
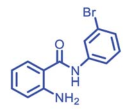
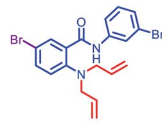
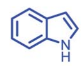
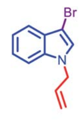
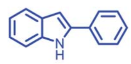
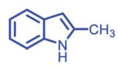
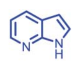
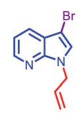
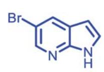
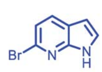
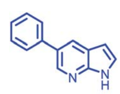
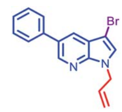
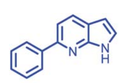
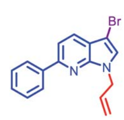
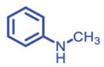
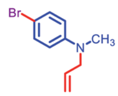
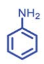
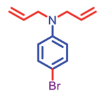
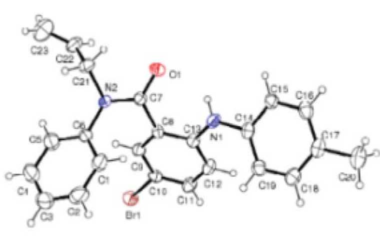
Entry	Substrate **1**	Substrate **2**	Product(s) (% yield)	
1	 **1a**	 **2a**	 **3a**(71)	—
2	 **1b**	2a	 **3b**(66)	**3b′**(33)
3	 **1c**	2a	 **3c**(67)	**3c′**(32)
4	 **1d**	2a	 **3d**(62)	**3d′**(36)
5	 **1e**	2a	 **3e**(64)	**3e′**(31)
6	 **1f**	2a	 **3f**(62)	—
7	 **1g**	2a	 **3g**(81)	—
8	 **1h**	2a	 **3h**(55)	—
9	 **1i**	2a	 **3i**(71)	—
10	 **1j**	2a	 **3j**(43)	—
11	 **1k**	2a	 **3k**(66)	—
12	 **1l**	2a	 **3l**(73)	—
13	 **1m**	2a	 **3m**(59)	—
14	 **1n**	2a	 **3n**(63)	—
15	 **1o**	2a	 **3o**(85)	—
16	 **1p**	2a	 **3p**(73)	—
17	 **1q**	2a	 **3q**(61)	—
18	 **1r**	2a	 **3r**(74)	—

Table 2 (*Contd.*)

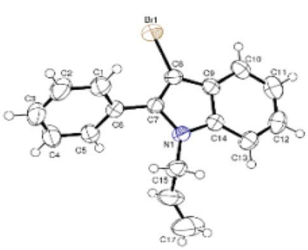
Table 2 (*Contd.*)

Entry	Substrate **1**	Substrate **2**	Product(s) (% yield)	
19	 **1s**	**2a**	 **3s**(52)	—
20	 **1t**	**2a**	 **3t**(62)	—

and mole equivalence of alkylating agent did not improve the yield (Table 1, entries 8 &10). On the other hand, the addition of the $CuBr_2$ as an additive in the reaction completely reversed the yields of the products as compound **4a** in 60% and compound **3a** in 30% yield (Table 1, entry 11). The reaction of **1a** with only $CuBr_2$ in DMSO, KOH furnished traces of product **4a** (Table 1, entry 12). Thus, $CuBr_2$ alone is not sufficient and allyl bromide **2a** is essential for the synthesis of dibromo compound **4a**. However, $CuBr_2$ improves the yield of brominated compound **4a** over **3a**. Evidently from the literature, this is due to $CuBr_2$ also acting as a bromide source.[32] The reactions in solvents such as dioxane, and CH_3CN afforded only allylated product **5a** in 80% and 85% yields, respectively (Table 1, entries 14 and 15). The absence of brominated products confirms the importance of DMSO solvent for the formation of BDMS species for bromination. To prove further that the formation of reactive species BDMS, experiments in dioxane and acetonitrile and several equivalents of DMSO were performed to yield the products minor **4a** and major compound **3a** without affecting the yield of the products (Table 1, entries 15 and 16). Thus, the condition shown in entry 4 of Table 1 was found to be optimum for allylated-brominated products and the condition shown in entry 9 was optimum for di/tetra brominated products. The additives were added to facilitate the bromination reaction.



3c



3l

Fig. 1 ORTEP diagram of compounds **3c** and **3l**.

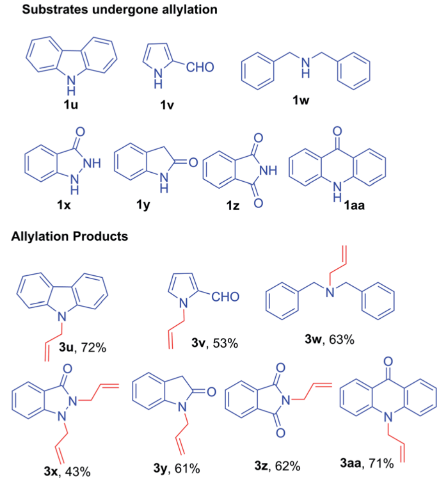
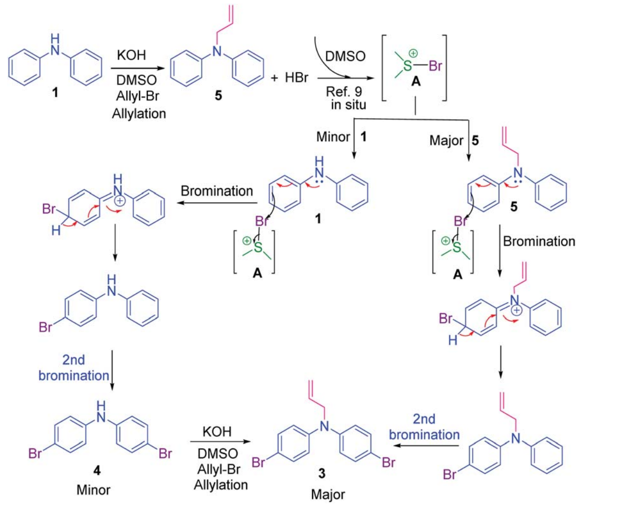


Fig. 2 Substrates undergo only allylation and the products.

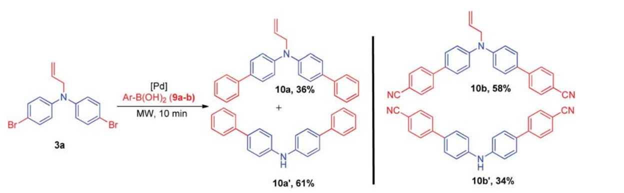
Having optimized condition in hand, the scope of the reaction DMSO–allyl bromide was explored to substituted aryl aminoamides **1b–j** or indole **1k–m** or 7-aza indole **1n–r** to afford corresponding *N*-allylated-brominated aryl aminoamides **3b–j** or indoles **3k–m** or 7-aza indoles **3n–r** in excellent yield (Table 2 and Fig. 1). It should be noted that in contrast to diphenylamine **1a**, substrates **1b–r** lead to products **3b–r**. Whereas, *N*1-arylated/alkylated, *N*2-arylated amino amides **1b–r** afforded the respective mono brominated/*N*1-mono allylated aryl aminoamides or indoles or 7-aza indoles **3b–r**. However, substrates **1b–d** afforded exclusively the mono brominated or *N*1, *N*2-diallylated aryl aminoamides **3b′–e′** in low yield. To widen the scope of the reaction, under optimized conditions, secondary amine with aryl alkyl substituents such as *N*-methyl aniline **1s** and primary amine such as aniline **1t** were also tested to afford products **3s** and **3t** in 52% and 62% yield, respectively. All the new compounds have been characterized by spectroscopic data and the representative compounds **3c** and **3l** were confirmed by XRD method (Fig. 1).[34]

On the other hand, under optimized condition, substrates such as 9*H*-carbazole **1u**, 2-formyl pyrrole **1v**, dibenzyl amine **1w**, pyrazolone **1x**, 2-oxindole **1y**, phthalimide **1z**, and acridin-9(10*H*)-one **1aa** afforded only the respective allylated products **3u–aa** in excellent yield (Fig. 2). The subsequent bromination was not observed due to the substrates are not suitable for aromatic electrophilic reaction with the reactive BDMS species to provide allylated–bromination products.

Based on the optimization and control experiments shown in Table 1, entries 4–7, 16, and 17, a plausible mechanism for the formation of compounds **3a** and **4a** is shown in Scheme 3. The key intermediate bromodimethyl sulfoniumion (BDMS)[9] plays a pivotal role for the brominated products *via* aromatic



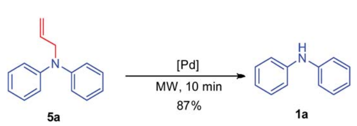
Scheme 3 Plausible mechanism for the formation of major compound **3a** and minor compound **4a**.



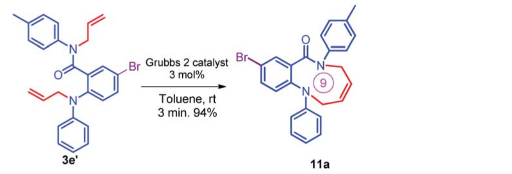
Scheme 4 Synthetic transformation of **3a** to **10a–b** and **10a′–b′**.

electrophilic substitution after initial allylation reaction of secondary amines. Thus, compound **3a** is believed to form *via* initially the base abstracts the proton attached to nitrogen in compound **1a**, and subsequent allylation leads to the formation of compound **5a.** Then the first electrophilic attack of BDMS intermediate **A** on **5a** leads to monobromo product followed by a second electrophilic attack on BDMS leads to *N*-allyl-bis(4-bromophenyl) amine **3a.** Whereas the *in situ* formed BDMS intermediate **A** upon simultaneous competitive bromination with compound **1a** affords compound **4a** and subsequent base initiated allylation forms the major product **3a.** However, upon completion of the reaction (TLC), a minor unreacted compound **4a** is isolated along with major product **3a.**

The synthetic utility of the compound **3a** has been demonstrated by Suzuki coupling.[25] Thus, a reaction between **3a** and phenylboronic acid **9a**, Pd(dppf)Cl_2. DCM and K_2CO_3 as base in dioxane : MeOH (3 : 1) solvent system was microwave (MW) irradiated (100 W) for 10 min to afford *N*-allyl-di([1,1′-biphenyl]-4-yl)amine **10a**, along with the unexpected deallylated product



Scheme 5 Deallylation of compound **5a**.



Scheme 6 Synthetic transformation of **3e′** to compounds **11a**.

di([1,1′-biphenyl]-4-yl)amine **10a′** in very good combined yield. Similarly, compounds **10b** and **10b′** were synthesized from the reaction of **3a**, 4-cyano phenylboronic acid **9b** (Scheme 4).

To substantiate the formation of deallylation products (**10a′–b′**) formed during competitive Heck coupling,[33] a model reaction was performed with allylated compound **5a** under similar reaction conditions, deallylation product **1a** was observed (Scheme 5).

Further, the synthetic utility of the compound **3e′** has been tested through the RCM protocol.[17] Thus, a solution of **3e′** in toluene, 3 mol% of Grubbs II catalyst afforded the (*Z*)-9-bromo-1-phenyl-6-(*p*-tolyl)-5,6-dihydro-1*H*-benzo[*b*][1,5]diazonin-7(2*H*)-one **11a** in 94% yield (Scheme 6). It should be noted that the highly functionalized derivative **11a** has been found in many natural products and could be synthesized *via* the short route reported herein.[35]

In conclusion, a mixture of DMSO–allyl bromide has emerged as a novel reagent for an atom economic one-pot method for the *N*-allylation/bromination of secondary aryl amines, aminoamides, indole, and 7-azaindole. A plausible mechanism has been proposed. The synthetic utility of the compound **3a** has been demonstrated by synthesizing *N*-allyl-di([1,1′-biaryl]-4-yl) amine **10a–b** along with the deallylated product **10a′–b′** *via* Suzuki coupling. A nine-membered diazonin-7(2*H*)-ones derivative **11a** has also been constructed from compound **3e′** *via* RCM protocol using Grubbs II catalyst.

Conflicts of interest

There are no conflicts to declare.

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