# Selective bromination of pyrrole derivatives, carbazole and aromatic amines with DMSO/HBr under mild conditions

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Bromination of pyrrole derivatives, carbazole and aromatic amines using the DMSO/HBr system affords high yields of the corresponding bromo compounds. Temperature control used in the bromination of anilines helped to promote selective formation of mono- or di-brominated products. Simple operation, low toxicity and high selectivity make this a promising new procedure for the bromination of aromatic compounds.

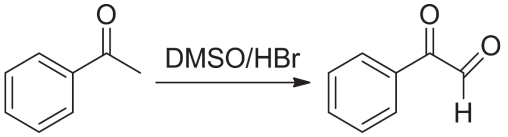
**Keywords:** bromination, DMSO/HBr, aromatic amines, bromodimethylsulfonium bromide, temperature control

Bromination of aromatic substrates is an important chemical transformation.[1–4] The bromo group in aromatic bromides can be converted into other functional groups efficiently and conveniently. Organic bromides have gained increasing importance commercially in the synthesis of various speciality chemicals such as pharmaceuticals, pesticides, insecticides, herbicides and natural products.[5–7]

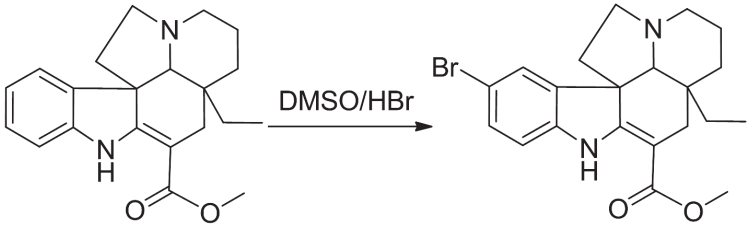
Various reagents have been developed for the bromination of aromatic compounds, such as $KBr/Bu_4NBr/HNO_3$,[8] KBr/Oxone,[9] $KBrO_3/H_2SO_4$,[4] $Br_2/SbF_3/HF$[10] and $NBS/SiO_2$.[11] The majority of these brominating procedures utilise potentially hazardous or oxidising agents.[12] From the perspective of 'green chemistry', therefore, it is essential to develop inexpensive, widely applicable, non-polluting, and more selective brominating reagents.[13,14] The DMSO/HBr system is widely applied in various reactions. It can be used as the oxidant for transforming acetophenones into arylglyoxals (Scheme 1).[15–19] Electrophilic aromatic bromination can be considered as a side reaction in several of these oxidations. For example, the treatment of indole alkaloids with DMSO/HBr led to a high yield of a halogenated product (Scheme 2).[15] In 1997, Majetich reported the bromination of aromatic substrates with DMSO/AcOH/HBr.[20] This system performed well in the bromination of phenol and anisole derivatives, but afforded low yields in the bromination of anilines. We now report an efficient procedure for the high yielding bromination of pyrrole derivatives, carbazole and aromatic amines using the DMSO/HBr system without the addition of any other acids. To the best of our knowledge, this is the first report of the application of DMSO/HBr to pyrrole derivatives and to a wide range of anilines.

## Results and discussion

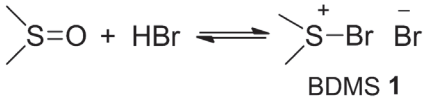
In our previous work, aryl methyl ketones such as acetophenone were smoothly transformed into arylglyoxals in DMSO/HBr.[21] However, 2-acetylpyrrole **2** was brominated to give 1-(4-bromo-1*H*-pyrrol-2-yl)ethanone **2a** in high yield in the same system.[27] We conjectured it an electrophilic aromatic bromination by bromodimethylsulfonium bromide (BDMS, **1**) formed in DMSO/HBr (Scheme 3), just like Majetich's bromination of phenols in DMSO/AcOH/HBr.[20] Further studies confirmed that the bromination did not occur in solvents other than DMSO (Table 1, entries 1–5). Moreover, the addition of acetic acid reduced the rate of bromination of 2-acetylpyrrole (Table 1, entry 6).




**Scheme 1**




**Scheme 2**




**Scheme 3**

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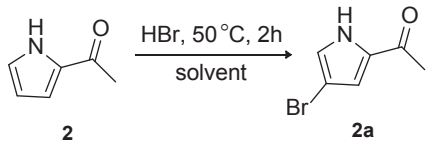
**Table 1** Yields of **2a** in different reaction conditions[a]




**2** **2a**

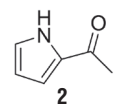
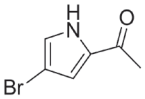
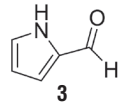
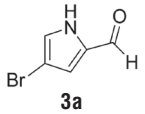
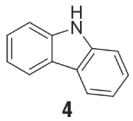
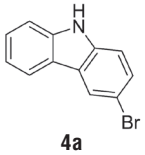
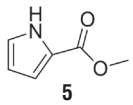
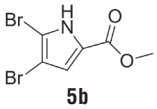
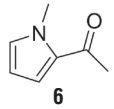
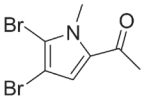
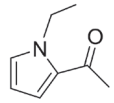
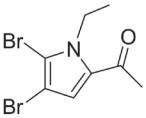
| Entry | Solvent | Yield of **2a**/%[b] |
|---|---|---|
| 1 | DMF | 0 |
| 2 | EtOAc | 0 |
| 3 | EtOH | 0 |
| 4 | acetonitrile | 0 |
| **5** | **DMSO** | **83** |
| 6 | AcOH/DMSO (2:1) | 21 |

[a]Reaction was performed with 1 mmol 2-acetylpyrrole (**2**) and 1 mL HBr in 1 mL solvent at 50 °C for 2 h.
[b]Isolated yield.

The successful bromination of 2-acetylpyrrole encouraged us to expand this reagent to other aza aromatic compounds. The results are shown in Table 2. Pyrrole-2-carboxaldehyde and carbazole were also efficiently monobrominated at 50 °C (Table 2, entries 2 and 3). The addition of an alkyl group into 2-acetylpyrrole mainly induced 4,5-dibromination (Table 2, entries 4–6), probably because of the activating nature of groups such as methyl and ethyl that facilitate dibromination.[22–24] The yield of compound **3a** gained through the DMSO/HBr system is higher than those obtained by traditional methods.[25,26]

According to Majetich *et al*.[20] the DMSO/HBr system was reported to effect the bromination of *N*,*N*-dimethylaniline with a yield of 43% after 24 h at room temperature. In the present work, *N*,*N*-dimethylaniline was *para*-monobrominated in DMSO/HBr system with a yield of 96% at 60 °C (Table 3, entry 1). Other tertiary amines, such as *N*,*N*-diethylaniline, *N*-phenylmorpholine and N-p*h*enylpiperazine were also efficiently *para*-monobrominated at 60 °C (Table 3, entries 2–4). When the *para*-position of the tertiary arylamine was blocked by a methyl group, *ortho*-monobromination occurred at 70 °C (Table 3, entry 5). With secondary or primary amines substrates, mono- or di-bromination could be achieved by regulating the temperature. At 50 °C, aniline and *N*-methylaniline were *para*-monobrominated; while at 80 °C, the main reaction was *ortho–para*-dibromination (Table 3, entries 6–9). With *o*-toluidine, monobromination occurred at the *ortho*-position at 50 °C whilst the main reaction was *ortho-para*-dibromination at 80 °C (Table 3, entries 10–11). *m*-Toluidine was also *para*-brominated at 50 °C (Table 3, entry 12). No obvious dibromination occurred at 80 °C. When the *para*-position of aniline was blocked by a methyl group, *ortho*-monobromination occurred at 50 °C and *ortho*-dibromination occurred at 80 °C (Table 3, entries 13 and 14). The above results indicate that in the DMSO/HBr system, bromination of aniline occurred first at the *para*-position and then at the *ortho*-position. Mono- and di-bromination of secondary and primary amines occurred at 50 °C and 80 °C respectively. To prove the practicality of this method for larger-scale synthesis, 4-bromo-*N*,*N*-dimethylaniline **8a** was prepared on a gram scale (10 mmol) to give a 95% yield of isolated product.

**Table 2** Bromination of aza aromatic compounds using DMSO/HBr[a]

| Entry | Substrate | Product | T/°C | Time/h | Yield/%[b] |
|---|---|---|---|---|---|
| 1 |  **2** |  **2a** | 50 | 2 | 83 |
| 2 |  **3** |  **3a** | 50 | 2 | 73 |
| 3 |  **4** |  **4a** | 50 | 2 | 87 |
| 4 |  **5** |  **5b** | 50 | 2 | 85 |
| 5 |  **6** |  **6b** | 50 | 2 | 91 |
| 6 |  **7** |  **7b** | 50 | 2 | 83 |

[a]Reaction was performed with 1 mmol substrate and 1 mL HBr in 1 mL DMSO at 50 °C for 2 h.
[b]Isolated yield.

## Conclusion

We have developed a highly efficient approach for the bromination of pyrrole derivatives, carbazole and aromatic amines with high yields. Temperature control used with primary and secondary amines helped to promote mono- or di-bromination. The reaction proceeds under mild conditions, and is amenable to the gram-scale synthesis of brominated anilines. Simplicity of operation, low toxicity and high selectivity make it a promising new bromination procedure.

## Experimental

All reagents and solvents were purchased from J&K Chemical Co. and used without further purification. Melting points were determined on a SGW X-4 micro melting point instrument. $^{1}$H and $^{13}$C NMR spectra were recorded on Varian 400 or Bruker 500 MHz spectrometers. IR spectra were obtained on a Perkin Elmer FTIR system. HRMS spectra were obtained using a LTQ Orbitrap Discovery spectrometer from Thermo Fisher.

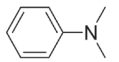
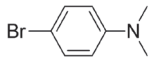
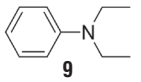
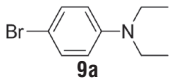
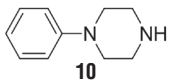
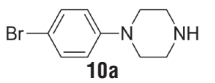
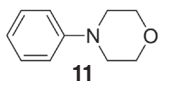
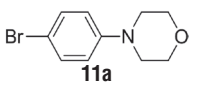
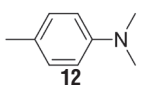
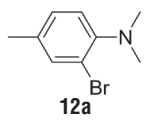
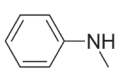
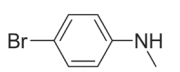
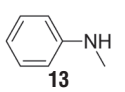
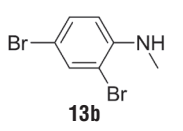
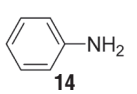
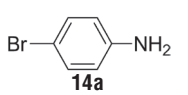
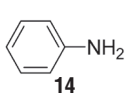
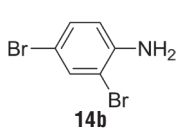
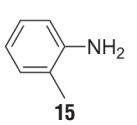
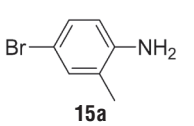
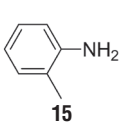
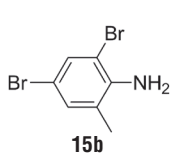
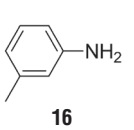
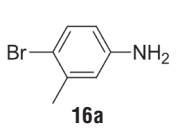
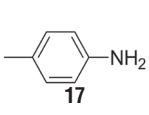
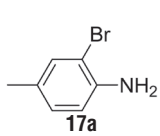
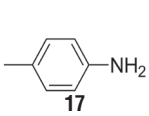
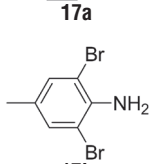
*Synthesis of bromination products: general procedure*

In a round-bottomed flask, the substrate (1 mmol) and aqueous HBr (48%) (1 mL) were mixed in DMSO (1 mL). The mixture was stirred at corresponding temperature for 1–4 h. After cooling to room temperature, the reaction was adjusted to pH 7–8 with aqueous NaOH solution (4 M). Then the mixture was washed twice with EtOAc, and the combined organic extracts were dried, filtered and concentrated under reduced pressure to give bromination products.

## Electronic Supplementary Information

The structure of compound **2a** was confirmed by X-ray crystallography. The details of the crystal data have been deposited with Cambridge Crystallographic Data Centre as Supplementary Publication, CCDC 890435. Full details of the physical and spectroscopic data ($^{1}$H and $^{13}$C NMR and HRMS) for all the compounds reported in this paper (Tables 2 and 3) and the X-ray crystal structure of **2a** is available as ESI through: stl.publisher.ingentaconnect.com/content/stl/jcr/supp-data

**Table 3** Bromination of aromatic amines using DMSO/HBr[a]

| Entry | Substrate | Product | T/°C | Time/h | Yield/%[b] |
|---|---|---|---|---|---|
| 1 |  **8** |  **8a** | 60 | 1 | 96 |
| 2 |  **9** |  **9a** | 60 | 1 | 95 |
| 3 |  **10** |  **10a** | 60 | 2 | 96 |
| 4 |  **11** |  **11a** | 60 | 1 | 97 |
| 5 |  **12** |  **12a** | 70 | 4 | 88 |
| 6 |  **13** |  **13a** | 50 | 2 | 76 |
| 7 |  **13** |  **13b** | 80 | 2 | 74 |
| 8 |  **14** |  **14a** | 50 | 2 | 75 |
| 9 |  **14** |  **14b** | 80 | 2 | 72 |
| 10 |  **15** |  **15a** | 50 | 2 | 82 |
| 11 |  **15** |  **15b** | 80 | 2 | 78 |
| 12 |  **16** |  **16a** | 50 | 2 | 79 |
| 13 |  **17** |  **17a** | 50 | 2 | 81 |
| 14 |  **17** |  **17b** | 80 | 2 | 77 |

[a]Reaction was performed with 1 mmol substrate and 1 mL HBr in 1 mL DMSO.
[b]Isolated yield.

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