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A novel tunable aromatic bromination method using alkyl bromides and sodium hydride in DMSO

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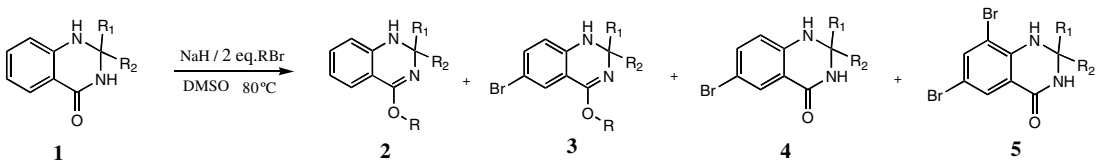
Abstract—Aromatic bromination on various aromatic systems with different substitutions was performed in the presence of alkyl bromide and sodium hydride in DMSO. Mono-bromination on a wide range of substrates was achieved by selecting proper alkyl bromides and controlling its amount. Further bromination could happen with more active alkyl bromides and additional amount of bromides and sodium hydride. The yields ranged from moderate to excellent. In addition, reaction mechanism was postulated to explain our observations.

Bromoarenes continue to be important synthetic intermediates for pharmaceutical and or other chemical related industries. The Suzuki coupling reaction[1] using bromoarenes as starting materials has fueled the development of efficient and selective bromination under milder conditions.[2–4] A variety of electrophilic bromination reagents include NBS/HBF_4–Et_2O, Br_2 in halogenated hydrocarbons or acetic acid, dioxane dibromide, pyridinum hydrobromide perbromide, DBU hydrobromide, tetra-alkyl ammonium tribromide, and bromodimethylsulfonium bromide [$(CH_3)_2SBr_2$],[5] which have been of choice for different substrates.[6] Herein, we wish to report a novel tunable aromatic bromination method for diverse set of substrates under basic conditions, using alkyl bromides and sodium hydride in DMSO.[7]

This bromination system was initially discovered in the course of investigating alkylating reaction of dihydroquinazolin-4-one **1**[8] with various alkyl halides including allyl chloride, allyl bromide, allyl iodide, 1-chloro-2-pentyne, and 1-bromo-2-pentyne, for the development of screening libraries. Besides alkylating reaction, an unexpected bromination reaction occurred to produce brominated by-products (compounds **3**, **4**, and **5**) when the reaction was run in DMSO at 80 °C with excess of alkyl bromide and nonnucleophilic base sodium hydride[9] (Scheme 1). The distribution of brominated products (**3**, **4**, and **5**) varied with different alkyl bromides used. However, chlorination or iodination did not occurred under the same reaction condition, while alkyl chlorides or alkyl iodides were used in place of bromide correspondingly.

It is noteworthy that Fletcher and Fan[10] reported the bromination of anilines in the presence of ethyl bromide in DMSO, but it required a much higher temperature (150 °C). In our case, bromination was observed only when DMSO was used as solvent and sodium hydride was used as base. Other bases, such as *t*-Bu^{t}OK, did



1 2 3 4 5

Scheme 1. Bromination of dihydroquinazolin-4-ones (**1**) with different alkyl bromides.

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Table 1. Unexpected formation of brominated products (percentage of components as determined by LC–MS using ELSD)

Entry	RX	Solvent/base	**2**	**3**	**4**	**5**
1	CH_2=$CHCH_2Cl$	DMSO/NaH	54	—	—	—
2	CH_2=$CHCH_2I$	DMSO/NaH	8	—	—	—
3	CH_2=$CHCH_2Br$	DMF/NaH	85	—	—	—
4	CH_2=$CHCH_2Br$	DMSO/*t*-BuOK	15	—	—	—
5	CH_2=$CHCH_2Br$	THF/*t*-BuOK	50	—	—	—
6	CH_2=$CHCH_2Br$	DMSO/NaH	—	8	77	
7	CH_3CH_2Br	DMSO/NaH	—	37	49	—
8	$PhCH_2Br$	DMSO/NaH	—	21	57	—
9	CH_3CH_2C≡CCH_2Br	DMSO/NaH	6	5	48	—
10	CH_3OCOCH_2Br	DMSO/NaH	—	—	18	10
11	$CH_3CH_2COCH_2Br$	DMSO/NaH	—	—	8	—

not induce bromination. Replacement of DMSO with DMF shut down the bromination as well. The results are summarized in Table 1.

The effect of alkyl bromides on the selectivity of bromination over alkylation was further investigated. Seven alkyl bromides representing a wide range of molecular weights, steric and electronic properties were selected. The reaction mixture was analyzed by LC–MS after 16 h at 80 °C, and the results are summarized in Table 2.

It is shown in Table 2 that secondary alkyl bromides in entries 2–8 eliminated the formation of alkylated products (**2**, **3**) due to increased steric hindrance in comparison to primary alkyl bromide in entry 1. In fact, monobrominated product **4** was formed exclusively in entries 2–4. Furthermore, introduction of ester group next to bromides resulted in di-bromination along with monobromination in entries 5 and 6. This indicated that electron withdrawing functionality increased the brominating reactivity. Increasing the amount of alkyl bromide eventually gave exclusively di-brominated product in entry 8. Regiochemistry of bromination was assigned by ^{1}H NMR.[11]

These results indicate that by using different alkyl bromide, we can generate bromination reagents with different bromination reactivity in situ. Thus by the variation of steric, electronic properties of alkyl bromides, in conjunction with the stoichiometry of the alkyl bromide used, we should be able to fine-tune the reactivity of the bromination reagent according to the reactivity of a particular aromatic system.

To further validate this tunable reactivity concept, we have extended this brominating system to other aromatic compounds with different reactivity toward bromination.

Firstly, 2-bromopentane was selected for bromination of other aromatic compounds. While phenyl, naphthanyl, and indolyl aromatic systems with electron rich directing substituents, such as amino groups and alkoxyl groups gave clean mono-brominated product, with regioselectivity and good to quantitative yields, as shown in Figure 1, attempts of bromination on alkyl, mono-alkoxyl substituted benzene, acetophenones, pyridine, pyrrole, and furan did not give controlled brominating products. Generally, nonactivated substrates with deficient electron density did not work under this set of condition.

Secondly, ethyl 2-bromopropionate was used to replace 2-bromopentane to enhance brominating reactivity, which led to successful bromination of those nonactivated substrates. Without changing other reaction conditions, mono-brominated products were generated with moderate to good yields, as shown in Figure 2.

Based on our experimental data, we propose the sequential events for the bromination reaction as depicted in Scheme 2.

We believe that bromophilic reaction[12] between DMSO and alkylbromide generates the active species for bromination in situ. DMSO is de-protonated by NaH, followed by reaction with alkyl bromide, to generate two intermediates: methyl alkyl sulfide and NaOBr. NaOBr can either react with sulfide intermediate and alkyl bromide to produce methyl sulfonium, or react with alkyl bromide to generate alkoxyhypobromite. These two intermediates were reported[5,13,14] to be active brominating reagents. It was conceivable that the

Table 2. Optimization toward bromination only condition (percentage of components as determined by LC–MS using ELSD)

Entry	RBr	Equiv	**2**	**3**	**4**	**5**
1	Bromoethane	3	—	37	49	—
2	2-Bromopropane	3	—	—	94	—
3	2-Bromobutane	3	—	—	93	—
4	2-Bromopentane	3	—	—	98	—
5	Methyl bromoacetate	3	—	—	63	33
6	Ethyl 2-bromopropionate	3	—	—	27	71
7	Ethyl 2-bromoisobutyrate	3	—	—	76	—
8	Ethyl 2-bromopropionate	4 or 5	—	—	—	95

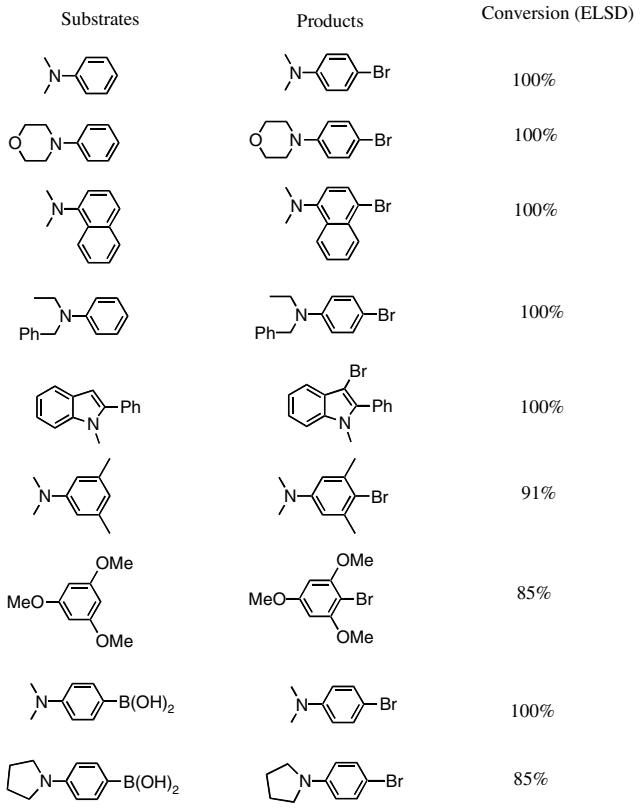


Figure 1. Bromination using 2-bromopentane.

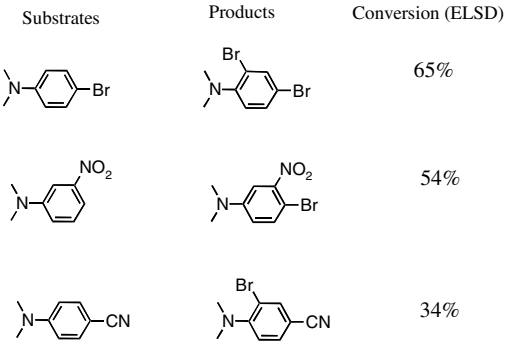
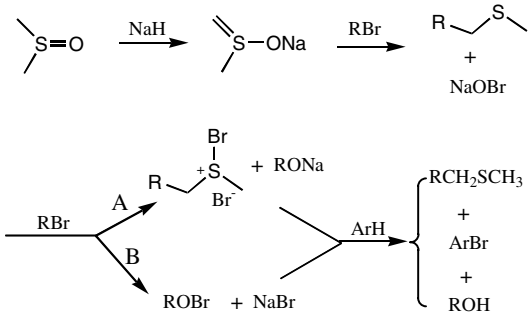
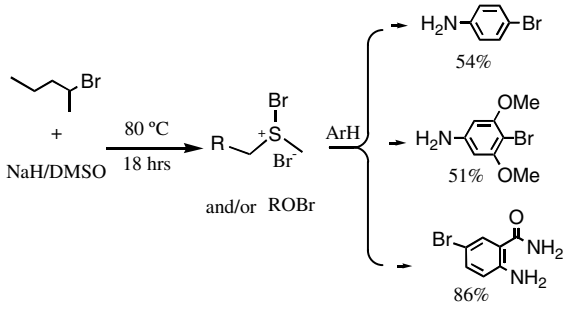


Figure 2. Bromination using ethyl 2-bromopropionate.



Scheme 2. In situ generation of bromination species.

brominating ability of these could be modulated by the alkyl group attached to them. Thus, this brominating system is tunable for different substrates by varying alkyl bromides.



Scheme 3. Bromination of unsubstituted aniline analogues.

To further support the proposed mechanism, two by-products of alkyl alcohol and methyl alkyl sulfide from the reaction were identified, by running the reaction in DMSO-d_6 and analyzing ^{1}H NMR and LC–MS data. They were further confirmed by HPLC isolation.[15]

To expand the limitation of solvents, and eliminating alkylation reaction, a two-step process was devised. The first step was to prepare the active brominating ingredient by heating bromides in DMSO in the presence of NaH. The second step was to add a solution of the substrate to the reaction. A list of solvents, including DMF, THF, ACN, EtOH, dioxane, or toluene, were tested to give the positive results shown in Scheme 3.

In conclusion, a novel tunable aromatic bromination method was developed using alkyl bromides and DMSO in the presence of NaH. The ability to modulate the brominating strength should warrant its applications in selective bromination on various aromatic systems.

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References and notes

1. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483; Suzuki, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley VCH, Verlag GmbH: New York, 1998; Chapter 2.
2. Smith, M. B. *Org. Lett.* **2002**, *4*, 2321–2323.
3. Okada, Y.; Yokozawa, M.; Akiba, M.; Oishi, K.; O-kawa, K.; Akeboshi, T.; Kawamura, Y.; Inokuma, S.; Nakamura, Y.; Nishimura, J. *Org. Biomol. Chem.* **2003**, *1*, 2506–2511.
4. Szurmigala, R. H. *J. Org. Chem.* **2004**, *69*, 566–569.
5. Majetich, G.; Hicks, R.; Reister, S. *J. Org. Chem.* **1997**, *62*, 4321–4326.
6. Oberhauser, T. *J. Org. Chem.* **1997**, *62*, 4504–4506, and references cited therein.
7. This work was presented at the 227th ACS National Meeting, Anaheim, CA. Abs. ORGN 159.
8. Yamato, M.; Horiuchi, J.; Takeuchi, Y. *Chem. Pharm. Bull.* **1981**, *29*, 3124–3129; Klemm, L. H.; Weakley, T. J. R.; Gilbertson, R. D.; Song, Y.-H. *J. Heterocycl. Chem.* **1998**, *35*, 1269–1273.

9. In a typical experiment, 100 μmol of compound **1** was dissolved in 500 μl DMSO and placed in a 2-dram vial. Different amounts (μl) of 0.6 M alkyl halide in DMSO were added according to the equivalents required, followed by a 500 μl suspension of 2% sodium hydride (60% suspended in mineral oil) in DMSO. The vial was capped and heated at 80 °C overnight (16 h) with shaking. Analytical samples were either directly taken from the reaction mixture or after work-up as follows: 3 ml DCM was added to the vial, followed by 2 ml of water; the aqueous phase was discarded after agitation and the DCM solution was washed twice with 2 ml of water.
10. Fletcher, T. L.; Pan, H. L. *J. Am. Chem. Soc.* **1956**, *78*, 4812.
11. ^{1}H NMR ($CDCl_3$): Compound **2** ($R^1 = R^2 = Et$): δ (ppm): 7.96 (1H, d, $J = 2.1$ Hz), 7.35 (1H, dd, $J = 2.1$, 8.4 Hz), 6.50 (1H, d, $J = 8.4$ Hz), 6.0 (1H, br s), 4.0 (1H, B), 1.75 (4H, q, $J = 7.5$ Hz), 0.96 (6H, t, $J = 7.5$ Hz). $C_{12}H_{15}BrNO_2$, 282.04, found, ES^+; 283, 285. Compound **3** ($R^1 = R^2 = Et$): δ (ppm): 7.94 (1H, d, $J = 2.8$ Hz), 7.63 (1H, d, $J = 2.8$ Hz), 6.82 (1H, S), 4.58 (1H, S), 1.78 (4H, q, $J = 7.5$ Hz), 0.97 (6H, t, $J = 7.5$ Hz); $C_{12}H_{14}Br_2NO_2$, 359.95; found ES^+: 361, 363, 365.
12. Zefirov, N. S.; Makhon'kov, D. I. *Chem. Rev.* **1982**, *82*, 615–624.
13. Kikuchi, D.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **1998**, *63*, 6023–6026.
14. Mach, M. H.; Bunnett, J. F. *J. Am. Chem. Soc.* **1974**, *96*, 936–938.
15. $EtOCOCH(CH_3)CD_2SCD_3$, MS 167.10, found M+ 168.15; ^{1}H NMR ($CDCl_3$): 4.25 (2H, q, $J = 6.9$ Hz), 3.56 (1H, q, $J = 6.9$ Hz), 1.42 (3H, d, $J = 6.9$ Hz), 1.30 (3H, t, $J = 6.9$ Hz); $EtOCOCH(CH_3)OH$, ^{1}H NMR ($CDCl_3$): 4.27 (2H, q, $J = 7.2$ Hz), 3.75 (1H, q, $J = 7.2$ Hz), 2.5 (1H, b), 1.57 (3H, d, $J = 7.2$ Hz), 1.32 (3H, t, $J = 7.2$ Hz).