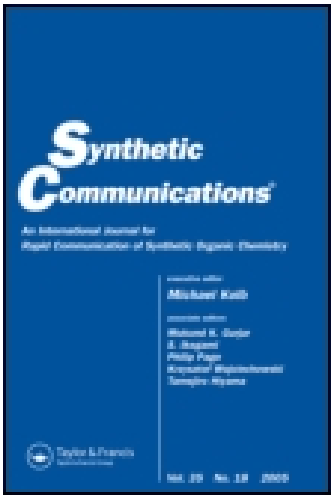

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Microwave-Assisted NBS Bromination of p-Iminotoluenes: Preparation of New Alcohol, Mercapto, and Amino Protection Groups

Sunil K. Upadhyay [a] & Branko S. Jursic [a b]
[a] Department of Chemistry , University of New Orleans , New Orleans , Louisiana , USA
[b] Stepharm , New Orleans , Louisiana , USA
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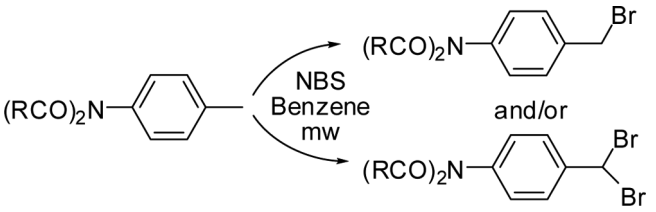
MICROWAVE-ASSISTED NBS BROMINATION OF *p*-IMINOTOLUENES: PREPARATION OF NEW ALCOHOL, MERCAPTO, AND AMINO PROTECTION GROUPS

Sunil K. Upadhyay[1] **and Branko S. Jursic**[1,2]
[1]*Department of Chemistry, University of New Orleans, New Orleans, Louisiana, USA*
[2]*Stepharm, New Orleans, Louisiana, USA*

GRAPHICAL ABSTRACT



Abstract *A simple, efficient, safe, high-yielding and rapid microwave-assisted method for the preparation of protected* p-*bromomethyl and* p-*dibromomethylanilines was developed as new alcohol, thiol, and amine protection groups. The procedure involves microwave-assisted* N-*bromosuccinimide (NBS) radical bromination of readily available* N-*protected* p-*toluidine. The microwave-assisted radical bromination was found to be superior to the conventional NBS radical bromination.*

Keywords Benzyl bromides; microwave-assisted reactions; NBS bromination; radical bromination

In the course of our preparations of the total synthesis of the naturally occurring antifungal C-27 steroidal saponins,[1–5] tetramic acid–based antibiotics,[6–9] and cysteine-tyrosine–based antioxidants,[10–12] we were faced with a significant problem involving the protection of hydroxyl, 1,3-dihydroxy, and thio groups. While there are numerous protection groups that are efficiently applied in the preparations of complex organic molecules,[13,14] our target molecules required additional functional properties that are not commonly associated with the traditional protection groups; namely, they must alter the physical properties of the protected molecules to produce intermediates that could be purified, characterized, and subjected to harsh reaction conditions. Additionally, we proposed that these protecting groups should also be

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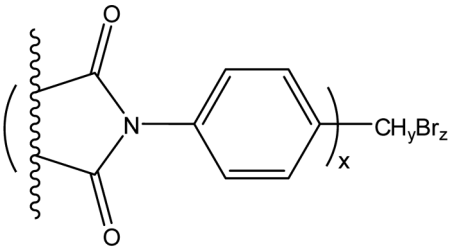
Address correspondence to Branko S. Jursic, Department of Chemistry, University of New Orleans, New Orleans, LA 70148, USA. E-mail: bsjstepharm@ymail.com

resistant to most reagents required for the preparation of our targeted natural products, allowing their convenient removal at the very end of the synthetic procedure.

We selected cyclic imides of *p*-aminobenzyl and *p*-aminobenzylidene bromides as ideal protection groups for the purposes of our natural product syntheses (Fig. 1). Cyclic imides are compounds that crystallize well and are relatively stable in acidic, neutral, and dry basic reaction media.[15] When these groups are part of the protected compound either in the ether, thioether, or amine form, they are relatively stable in the mentioned reaction conditions. The major advantage of these benzyl-based protection groups over others that their acid sensitivity can be significantly increased by removal of imide protection using hydrazine or a base. The resulting p-amino benzyl ethers, thioethers, or amines are easily cleaved with moderate acids. For alcohols, the corresponding phenylmethyl bromide **1** is an ideal protection group, whereas for 1,2- and 1,3-diols the phenylmethylene dibromide **2** is the ideal protection group. Finally, for thiols and amines, the triphenylmethyl bromide **3** is the ideal protection group (Fig. 1).[16–18]

One of the requirements for broad use of these protection groups in natural product synthesis is that they be available in large amounts, either commercially or through simple preparation procedures. The classical approach to prepare benzyl bromides and benzylidene dibromides is through the direct bromination of the benzylic methyl or through deoxybromination of benzylic alcohol or benzaldehyde derivatives.[19] The latter route implies a multistep synthesis, which is often time-consuming. Alternatively, the two-step bromination method, via the generation of the methyl anion developed by Fraser,[20,21] appears attractive. However, this method is incompatible with the presence of nucleophile-sensitive functional groups on the molecule, such as an ester group.

Radical-mediated bromination is frequently used to achieve selective activation of the benzyl and allyl positions of an organic molecule.[22] The reaction is normally carried out using *N*-bromosuccinimide (NBS) in tetrachloromethane with various radical initiators.[23] However, tetrachloromethane presents relatively high toxicity and carcinogenicity, which restricts its use in general synthesis.[24] Tetrachloromethane can be replaced by other solvents, such as methyl acetate, in light and some microwave-assisted benzylic brominations,[25] but to avoid using tetrachloromethane, Golding and coworkers[26] used (trifluoromethyl)benzene as a solvent in



1: x = z = 1; y = 2 for alcohol protection
2: x = y =1; z = 2 for 1,2- and 1,3-diols protection
3: x = 3, y = 0, z = 1: for thiol and amino group protection

Figure 1. New alcohol, thiol, and amino protection groups.

the benzylic bromination with NBS. Subsequently, Ulrich and coworkers found that dichloromethane and benzene are better solvents for radical bromination than carbontetrachloride.[27]

In a recent approach, radical benzyl bromination was performed using H_2O_2-HBr. This is a promising synthetic procedure,[28] but the reagent pair is still somewhat aggressive. The softer and simplest route to prepare these compounds remains the free radical bromination with NBS.[29–31] Nonetheless, some of these brominations require long reaction times (more than 20 h of refluxing) that cause product decomposition and the formation of a dibromo by-product that is often difficult to separate from the product. Nevertheless, we selected NBS radical bromination of cyclic imides protected *p*-toluidene as our method of choice to prepare our necessary reagents (compounds **1**–**3**, Fig. 1). Two major recent developments enabled us to properly explore this reaction. First, we developed a laboratory microwave reactor that can be used as standard laboratory equipment for reactions that require high energy, and second, this equipment was recently used to prepare large quantities of cyclic imides in short reaction times and good yields.[32] Because of these two advances in our laboratory, the starting material for the preparation of new protection groups was already available in large quantities.

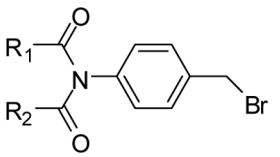
Considering that the NBS radical benzyl bromination usually requires longer reaction times, there have been previous attempts to shorten the NBS benzyl bromination and increase the bromination selectivity. As mentioned previously, there were other attempts to perform microwave-assisted benzyl bromination in methyl acetate.[25] However, the isolated yields of the reaction were, at best, moderate (30–60%). On the other hand, Goswami and coworkers reported microwave-assisted benzyl bromination without solvent and a radical initiator.[33] This reaction was performed using a microwave magnetron power of 450 W for several minutes. The reported yields for this experimental procedure were around 40%. In another recent report, the microwave-assisted benzyl bromination was compared to ultrasound-assisted benzyl bromination.[34] In this experiment, the microwave reaction conditions were strenuous (microwave temperature 150 °C, time 4 min, pressure 3.5 bar, and microwave magnetron power 200 W) and clearly results in the reactant decomposition and poor yields of the brominated product. Subsequently, the bromination reaction mixture contained substantial amounts of the dibromination product, causing additional problems with purification. Using the microwave reactor developed in our laboratory, we were able to extend the reaction times associated with organic reactions by controlling the temperature and adding magnetic stirring and a water-cooled condenser. In doing these simple modifications, we were able to extend the length of the reaction time to several days if necessary, below or at solvent refluxing temperature.

Our microwave-assisted NBS bromination was performed in benzene as solvent instead of tetrachloromethane with only 1 equivalent of NBS. The reaction was basically over in less than 2 h, and the isolated yields were greater than 80% (Table 1). By comparison, if the reaction was performed under conventional methods (refluxing of benzene), then the reaction required a reaction time 3–10 times longer. Longer reaction times generate more by-products that hamper the isolation and purification of the final product, resulting in lower isolated yields. In addition, for conventional NBS bromination, more than 1 equivalent (1.3–1.5 eq.) of NBS

Table 1. Preparation of benzyl bromides

	Microwave		Conventional	
Product	Time (min)	Yield (%)	Time (min)	Yield (%)
4a	30	85	190	72
4b	40	83	300	75
4c	60	87	180	65
4d	40	80	240	67
4e	90	82	300	78

is required for full conversion (disappearance of starting material). On the other hand, if carbon tetrachloride was used as a solvent, then the required reaction time was more than doubled in comparison with benzene as a solvent. For instance, 17 h was required for the preparation of **4a** in benzene (Table 1). For example, to shorten reaction times to 2 h for compound **4a** (Table 1) using more conventional reaction conditions, a combination of both carbon tetrachloride refluxing and ultraviolent radiation was used.[35] These examples only emphasize superiority of microwave-assisted NBS benzyl bromination in benzene as a solvent (Table 1).



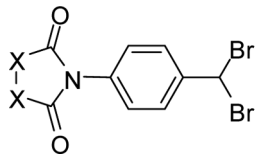
4a: R_1-R_2 = 1,2-C_6H_4; **4b**: R_1-R_2 = CH_2CH_2;
4c: R_1-R_2 = 1,8-$C_{10}H_6$; **4d**: R_1 = C_6H_5, R_2CO = CH_3
4e: ortho isomer of **4a**

Microwave-assisted NBS dibromination is as effective as monobromination (Table 2), and this method again is superior, considering that the usual isolated yields for dibromination are between 5% to 40%.[36] Furthermore, using conventional methods, the reaction mixture always contains mixture of dibromo and monobromo products and requires more than 1 day to complete and at least 3 equivalents of NBS. In the case of conventional heating, the benzene solution was refluxed for at least 12 h and a small amount of monobrominated product was still present. The isolated yields are somewhere between 60% and 70%.[37] Microwave-assisted reaction requires only a few hours with more than 95% conversion into dibromo product,

Table 2. Isolated yields of benzylidine bromides

	Microwave		Conventional	
Product	Time (h)	Yield (%)	Time (h)	Yield (%)
5a	1	88	12	70
5b	3	83	24	65
5c	3	92	24	66

and the isolated yields are between 80% and 90% (Table 2). This is the cleanest, simplest, shortest, and the highest-yielding procedure for preparation of dibromomethylarene derivatives from methylarenes.



5a: n = 1, X-X = 1,2-C_6H_4
5b: n = 1, X-X = CH_2CH_2
5c: n = 1, X-X = 1,8-$C_{10}H_6$

Finally, benzyl NBS bromination can be performed in environmentally friendly solvents such as ethyl acetate and diethyl carbonate.[23] For instance, if NBS radical bromination was performed in ethyl acetate instead of benzene for **4a** (Table 2), then the required reaction time was slightly longer (1 h), and the isolated yield is moderately lower (75%). However, if the NBS bromination was performed in dimethylformaide (DMF) as a reaction media, then the reaction was completed in 10 min but isolated yield was only 60%.

In conclusion, it can be stated that with using this new NBS radical benzyl bromination method, desirable bromomethyl and dibromomethylarenes can be prepared from readily available methylarenes in good quantities and short reaction times coupled with almost quantitative isolated yields. This synthetic approach was proven to be superior to conventional NBS bromination.[38,39]

EXPERIMENTAL

Thin-layer chromatographic analysis (TLC) was performed using silica gel on glass plates and was detected under ultraviolet (UV) light. The ^1H and ^{13}C NMR spectra were run on Varian 300-MHz Gemini2000 and on Varian 400-MHz Unity instruments in $CDCl_3$ solvent and internal standards. The mass spectra were recorded on a Micromass Quattro 2 Triple Quadrupole mass spectrometer. All reagents and solvents were purchased from Aldrich and were analytical grade. The laboratory version of our microwave has a cavity size of 21.6 cm high, 17.30 cm wide, and 25.4 cm deep with two 2.54-cm holes on the top of the microwave for the condenser and thermometer. The magnetron (700 W) was directly wired to a variable electronic autotransformer for control of the magnetron power. An ECM meter (10 amps) was wired to the magnetron transformer to control the microwave power. The magnetic stirrer was installed beneath the cavity for stirring the reaction mixture. The reaction temperature was measured directly with a thermometer inserted into the reaction mixture.

Typical Procedure for Preparation of Monobromoarene 4

Benzene (10 ml) solution of methyl benzene derivative (5 mmol), *N*-bromosuccinamide (0.89 g; 5 mmol), and benzoylperoxide (0.12 g; 0.5 mmol) was refluxed under microwave heating (magnetron power 600 W). After reaction was completed (see Table 1) the solvent was evaporated; the solid residue was dissolved

in dichloromethane (100 ml) and washed with saturated water solution of sodium bicarbonate (3×15 ml) and water (3×15 ml). Dichloromethane was evaporated, and the solid residue was purified by silica-gel column chromatography with hexane–dichloromethane as an eluent.

Selected Data for 4a–4e

2-(4-(Bromomethyl)phenyl)isoindoline-1,3-dione (4a). Isolated yield (85%). ^{1}H NMR δ 7.98 (2H, m), 7.80 (2H, m), 7.55 (2H, d, $J = 8$ Hz), 7.45 (2H, d, $J = 8$ Hz), and 4.55 (2H, s) ppm. ^{13}C NMR δ 167, 140, 138, 135, 132, 130, 127, 124, and 33 pm. $C_{15}H_{10}BrNO_2$ (MW 316.15). MS (m/z) 317.99 (10%), 314.99 (100%), and 316.99 (95%).

1-(4-(Bromomethyl)phenyl)pyrrolidine-2,5-dione (4b). Isolated yield 83%. ^{1}H NMR δ 7.51 (2H, d, $J = 7.6$ Hz), 7.32 (2H, d, $J = 7.6$ Hz), 4.48 (2H, s) ppm. ^{13}C-NMR δ 176, 138, 130, 127, 126, 33, and 28 ppm. $C_{11}H_{10}BrNO_2$ (MW 268.11). MS (m/z) 269.99 (8%), 268.99 (95%), 266.99 (100%).

2-(4-(Bromomethyl)phenyl)-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (4c). Isolated yield (87%). ^{1}H NMR δ 8.65 (2H, d, $J = 7.2$ Hz), 8.27 (2H, d, $J = 8.4$ Hz), 7.80 (2H, t, $J = 7.2$ Hz), 7.58 (2H, d, $J = 8.4$ Hz), 7.30 (2H, d, $J = 8.4$ Hz), and 4.57 (2H, s) ppm. ^{13}C NMR δ 164, 138, 135, 134, 131, 130, 129, 127, 123, and 33 ppm. $C_{19}H_{12}BrNO_2$ (MW 366.21) m/z: 368.01 (15%), 367.00 (100%), 365.01 (100.0%), 366.01 (10%).

***N*-(4-(Bromomethyl)phenyl)-*N*-methylbenzamide (4d).** Isolated yield (80%). ^{1}H NMR δ 7.28 (2H, d, $J = 7.8$ Hz), 7.25 (7H, m), 7.02 (2H, d, $J = 7.8$ Hz), 4.40 (2H, s), and 3.47 (3H, s) pp. ^{13}C-NMR δ 171, 145, 136, 135, 130, 129, 128, 127, 39, and 33 ppm. $C_{15}H_{14}BrNO$ (MW 304.18). MS (m/z) 306.03 (10%) 305.02 (90%), 303.03 (100).

2-(2-(Bromomethyl)phenyl)isoindoline-1,3-dione (4e). Isolated yield (82%). ^{1}H NMR δ 7.98 (2H, m), 7.80 (2H, m), 7.30 (4H, m), and 4.46 (2H) ppm. ^{13}CNMR δ 167, 136, 135, 132, 131, 130, 129, 128, 124, and 30 ppm. $C_{15}H_{10}BrNO_2$ (Mw 316.15). MS (m/z) 317.99 (10%), 316.99 (95%), 314.99 (100%).

Typical Procedure for Preparation of Dibromoarene 5

Benzene (10 ml) mixture of the methylbenzene derivative (3.3 mmol), *N*-bromsucinimide (1.8 g; 10 mmol), and benzoylperoxide (75 mg; 0.31 mmol) was refluxed for 3 h under microwave radiation (magnetron power 600 W). The solvent was evaporated under reduced pressure, and the solid residue was dissolved in dichloromethane (100 ml). Dichloromethane solution was washed with saturated sodium bicarbonate (3×15 ml), and water (3×20 ml) and dried over anhydrous sodium sulfate. The solvent was evaporated, and the residue was purified by filtration through a short silica-gel column with hexane–dichloromethane as solvent.

Selected Data for 5a–5c

2-(4-(Dibromomethyl)phenyl)isoindoline-1,3-dione (5a). Isolated yield (88%). ^{1}H NMR δ 7.98 (2H, m), 7.82 (2H, m), 7.72 (2H, d, $J = 8.0$ Hz), 7.51 (2H, d, $J = 8.0$ Hz), and 6.68 (1H, s) ppm. ^{13}C-NMR δ 167, 141, 135, 133, 131, 128, 127, 124, and 40 ppm. $C_{15}H_9Br_2NO_2$ (MW 395.05). MS (m/z) 396.90 (50%), 395.90 (10%), 394.90 (100%), 392.90 (50%).

1-(4-(Dibromomethyl)phenyl)pyrrolidine-2,5-dione (5b). Isolated yield (83%). ^{1}H NMR δ 7.68 (2H, d, $J = 7.4$ Hz), 7.32 (2H, d, $J = 7.4$ Hz), 6.64 (1H, s), and 2,99 (4H, s) ppm. ^{13}C NMR δ 178, 133, 128, 127, 126, 40, and 28 ppm. $C_{11}H_9Br_2NO_2$ (MW 347.00) m/z 348.90 (50%), 347.90 (10%), 346.90 (100%), 344.90 (50%).

2-(4-(Dibromomethyl)phenyl)-1*H*-benzo[de]isoquinoline-1,3(2*H*)-dione (5c). Isolated yield (92%). ^{1}H NMR δ 8.82 (2H, t, $J = 8$ Hz), 8.48 (2H, d, $J = 8$ Hz), 7.83 (2H, t, $J = 8$ Hz), 7.75 (2H, d, $J = 7.8$ Hz), 7.36 (2H, d, $J = 7.8$ Hz), and 6.72 (1H, s) ppm. ^{13}C NMR ($CDCl_3$, 400 MHz) δ 164, 142, 137, 135, 132, 129, 128, 127, 123, and 40 ppm. $C_{19}H_{11}Br_2NO_2$ (MW 445.10). MS (m/z) 447.91 (10%), 446.9 (50%) 445.9 (20%), 444.9 (100%), 443.9 (10%). 442.9 (50%).

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