AN EFFICIENT AND REGIOSELECTIVE BROMINATION OF AROMATIC AMINES AND PHENOLS USING LANTHANUM(III) NITRATE HEXAHYDRATE AS A CATALYST

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A simple, highly efficient and economic method for the mono-bromination of number of aromatic amines and phenols using $La(NO_3)_3{\cdot}6H_2O$ as a catalyst is explained. The protocol is regioselective, high-yielding and applied at room temperature to a number of aromatic amines and phenols having electron donating or withdrawing substituents.

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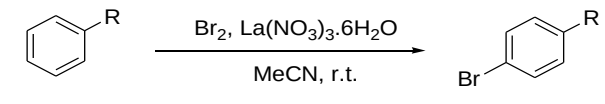
Introduction

The brominated aromatic compounds have been widely utilized as starting materials and intermediates in the production of pharmaceuticals, agrochemicals and speciality chemicals.[1,2] Moreover it is also known that they can form C-C bond via trans-metalation/cross-coupling reactions such as Stille,[3] Suzuki,[4-8] Heck,[9-12] Sonogashira,[13,14] Ullmann[15] and Wurtz reaction. A well-known method for preparation of brominated aromatic compounds is the reaction with elemental bromine in the presence of transition metal based catalyst.[16-17] Several methods have been reported in the past for the bromination of aromatic compounds which uses reagents such as Br_2-Lewis acids,[18] NBS-H_2SO_4-CF_3CO_2H,[19] NBS-NaOH,[20] NBS-SiO_2,[21] Br_2-Al_2O_3,[22] NBS-Amberlyst,[23] NBS-H-form zeolite-5 (HZSM-5),[24] tert-BuOOH or H_2O_2-HBr,[25] NBS-sulfonic-acid-functionalized silica,[26] NBS/BF_3-H_2O,[27] NBS-NH_4OAc,[28] NBS-tetraethyl ammonium bromide,[29] NBS-$Pd(OAc)_2$,[30] NBS-PTSA,[31] hexamethylenetetramine-Br_2,[32] Br_2/SO_2Cl_2/Zeolite[33] tribromoisocyanuric acid,[34] bromodichloroisocyanuric acid,[35] NH_4VO_3-H_2O_2-HBr,[36] NaBr-$PhI(OAc)_2$[37] and $CuBr_2$.[38] However some of these methods suffer from poor selectivity, use of expensive reagents and formation of polysubstituted products.

The major concern with aniline or phenol derivatives is that these active systems tend to undergo mono to poly bromination, when treated with elemental bromine under usual bromination conditions.[16,17,39] Therefore, it's challenging to perform selective mono-bromination of these compounds. In order to overcome the problem only few improved protocols have been reported in literature, for example, the combination of aqueous TBHP or H_2O_2 together with hydrohalic acid,[40] use of n-BuLi and R_3SnCl,[41] etc. but still these methods have certain limitations like use of harsh reaction conditions, low yields of the products, etc. Therefore there is a pressing need of protocol which can offer selectivity as well as better yields using simple reaction conditions. The chemistry of $La(NO_3)_3{\cdot}6H_2O$ as a catalyst for various types of reactions on number of substrates is well-exploited by Y. Venkateswarlu.[42] This catalyst is a mild, inexpensive, comparatively non-toxic, readily available, easy to handle and insensitive to air. This encouraged us to use this mild Lewis acid catalyst for the bromination of amines and phenols.

Herein we describe an economic, efficient and regioselective mono-bromination method for activated aromatic amines and phenols using cheaper and safe Lanthanum (III) nitrate hexahydrate [$La(NO_3)_3{\cdot}6H_2O$]. The reaction proceeds at ambient conditions while offering excellent yields of the products. The reaction parameters study show that it requires short time and most of the anilines and phenols were converted immediately.



Scheme 1. Bromination of aromatic amines and phenols using $La(NO_3)_3{\cdot}6H_2O$.

Experimental

All chemicals and reagents were purchased from commercial suppliers and used without purification. Aromatic amines and phenols were purchased from Across organics, Lanthanum (III) nitrate hexahydrate ($La(NO_3)_3.6H_2O$), liquid bromine and silica gel for column chromatography (230-400 mesh) from Aldrich, acetonitrile (CH_3CN) from Merck and ethyl acetate, sodium sulphate (Na_2SO_4), and NaCl were purchased from Fisher Scientific.

The melting points of the products are uncorrected. The ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance spectrometer operating at 300 MHz for ^1H and 100 MHz for ^{13}C nuclei, respectively at 295 K in $CDCl_3$. The chemical shifts were assigned in comparison with the residual proton and carbon resonance of the solvent $CDCl_3$ (δ H = 7.25 ppm, δ_C = 77.0 ppm) and tetramethylsilane (TMS) as the internal reference. MS analysis was done on an APEX 2 spectrometer from Bruker Daltonic with electrospray ionization (ESI) method. FTIR spectra were recorded on Bruker Vertex-70 spectrometer in the range of 400-4000 cm^{-1} and peak positions are given as transmittance (%) against wave numbers (cm^{-1}).

General procedure for bromination of aromatic amines and phenols

In a single-neck round bottom flask, a solution of aniline or phenol (1.47 mmol) in CH_3CN was taken and to this $La(NO_3)_3{\cdot}6H_2O$ (1.47 mmol) was added in one portion. To this mixture, liquid Br_2 (1.47 mmol) diluted in 2 mL CH_3CN was added drop wise at room temperature. The progress of the reaction was monitored by thin layer chromatography (TLC). After completion of the reaction, solvent was evaporated under reduced pressure and water was added to the residue and the mixture was extracted with ethyl acetate (3×10 mL). The combined ethyl acetate layers were washed with saturated solution of $NaHCO_3$ and NaCl, dried over Na_2SO_4, concentrated under vacuum and subjected to column chromatography for purification using ~10% ethyl acetate-hexane solvent system to obtain pure brominated aniline or phenol.

Spectral data of selected compounds

4-Bromoaniline (Table 1, entry 1): IR: 3472, 3379, 1615, 1489, 1282 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.60 (br s, 2H), 6.61 (d, *J*=6.5 Hz, 2H), 7.32 (d, *J*=6.9, 2H). MS (m/z): 173.

2-Bromo-4-methylaniline (Table 1, entry 4): IR: 3464, 3372, 3012, 2912, 1614 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.21 (s, 3H), 3.94 (br s, 2H), 6.62 (d, *J*=0.8 Hz, 1H), 6.91 (d, *J*=2.4 Hz, 1H), 7.20 (s, 1H). MS (m/z): 187.

4-Bromo-2-chloroaniline (Table 1, entry 5): IR: 3423, 3328, 3220, 2924, 1622, 1484 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.51 (br s, 2H), 7.09 (m, 3H).

4-Acetyl-2-bromoaniline (Table 1 entry 7): ^1H NMR (300 MHz, $CDCl_3$): δ 7.99 (d, *J*=2.0 Hz, 1H), 7.66 (dd, *J*=8.0, 2.0 Hz, 1H), 6.70 (d, *J*=8.0 Hz, 1H), 4.82 (br s, 2H), 2.46 (s, 3H). MS (m/z): 215, 213.

2-Amino-5-bromopyridine (Table 1, entry 9): IR: 3402, 3186, 1650, 1569, 1485 cm^{-1}. ^1H NMR (300 MHz, DMSO): δ 6.82 (br s, *J*=1 Hz, 2H), 8.24 (s, 2H); ^{13}C NMR (100 MHz, DMSO): 104.2, 155.2, 159.0, 161.7. MS (m/z): 175.

2-Amino-5-bromo-3-methylpyridine (Table 1 entry 10): ^1H NMR (300 MHz, $CDCl_3$): δ 2.01 (s, 3H), 5.02 (br s, 2H), 7.32 (d, *J*=2.0 Hz, 1H), 7.85 (d, *J*=2.0 Hz, 1H). MS (m/z): 188, 186.

2-Amino-1-bromonaphthalene (Table 1, entry 12): ^1H NMR (300 MHz, $CDCl_3$): δ 5.75 (br s, 1H), 7.41-7.62 (m, 4 H), 7.81-7.93 (m, 2H). MS (m/z): 224.

4-Bromo-2-methylphenol (Table 2 entry 2): ^1H NMR (300 MHz, $CDCl_3$): δ 2.18 (s, 3H,), 4.86 (br s, 1H), 6.56 (d, *J*=8.0 Hz, 1H), 7.10 (dd, *J*=8.0, 2.0 Hz, 1H), 7.18 (d, *J*=2.0 Hz, 1H). MS (m/z): 188, 186.

4-Bromo-3-methylphenol (Table 2, entry 3): ^1H NMR (300 MHz, $CDCl_3$): δ 2.31 (s, 3H), 5.28 (br s, 1H), 6.54 (dd, *J*=8.55, 2.81Hz, 1H), 6.72 (d, *J*=2.81 Hz, 1H), 7.32 (d, *J*=8.55, 1H).

3-Bromo-4-hydoxy-5-methoxybenzaldehyde (Table 2 entry 8): ^1H NMR (300 MHz, $CDCl_3$): δ 3.96 (s, 3H), 7.28 (s, 1H), 7.59 (s, 1H), 9.72 (s, 1H), 10.01 (br s, 1H). MS (m/z): 232, 230.

1-Bromo-2-napthol (Table 2, entry 10): ^1H NMR (300 MHz, $CDCl_3$): δ 5.73 (br s, 1H), 7.42-7.61 (m, 4H), 7.82-7.92 (m, 2H). MS (m/z): 224.

1-Bromo-3-methoxy-2-napthol (Table 2, entry 11): ^1H NMR (300 MHz, $CDCl_3$): δ 3.43 (s, 3H), 5.61-5.74 (br s, 1H), 7.31-7.54 (m, 4H), 7.63 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 105.3, 119.0, 122.5, 126.1, 127.0, 133.4, 145.0. MS (m/z): 254.

Results and Discussion

Firstly, aniline was chosen as a model substrate to find out optimal reaction conditions. We varied several reaction parameters to optimize the reaction conditions, including the amount of the catalyst $La(NO_3)_3{\cdot}6H_2O$, brominating agent, reaction temperature and use of different solvents. The optimum reaction conditions are when aniline (1.47 mmol), $La(NO_3)_3{\cdot}6H_2O$ (1.47 mmol) and Br_2 (1.47 mmol) were reacted for just 3 minutes at room temperature, 84% of the 4-bromoaniline was obtained. The reaction was carried out in various protic and aprotic solvents and acetonitrile (CH_3CN) was found to be the most suitable one. Also it is well known that bromination and chlorination reactions are more challenging compare to iodination because of lower nucleophilicity of the bromide and chloride than iodide. Considering this acetonitrile, apolar aprotic solvent is effective for bromination of anilines and phenols.

The effectiveness of the catalyst $La(NO_3)_3{\cdot}6H_2O$ was studied by performing the reaction of aniline with elemental bromine in the presence and absence of catalyst. In the presence of catalyst the reaction was complete in just 3 min whereas without the catalyst the reaction was not completed even after 24 h. The use of the catalyst significantly reduced the reaction time along with the enhancement in the yield. The bromination was carried out with different aniline derivatives having electron donating or withdrawing substituents. It was generally observed that when aniline has electron donating substituents (Table 1, entry 1-4), the yield of the mono-brominated product was more compared to one having electron withdrawing groups (Table 1, entry 5-8). Similar trend was also observed in the cases of phenols (Table 2).

Table 1. Bromination of aromatic anilines using $La(NO_3)_3{\cdot}6H_2O$ at room temperature.

S. No.	Substrate	Time (min)	Product	Yield (%)	Mp. (°C)
1	Aniline	3	4-Bromoaniline	84	61-63
2	N-Methylaniline	4	4-Bromo-N-methylaniline	80	54-56
3	N,N-Dimethylaniline	10	4-Bromo-N,N-dimethylaniline	83	53-56
4	4-Methylaniline	7	2-Bromo-4-methylaniline	81	27-29
5	2-Chloroaniline	4	4-Bromo-2-chloroaniline	78	68-72
6	4-Chloroaniline	5	2-Bromo-4-chloroaniline	75	64-66
7	4-Acetylaniline	3	4-Acetyl-2-bromoaniline	73	155-158
8	4-Aminobenzoic acid	13	4-Amino-3-bromobenzoic acid	72	211-215
9	2-Amino-pyridine	8	2-Amino-5-bromopyridine	84	135-138
10	2-Amino-3-methylpyridine	10	2-Amino-5-bromo-3-methyl-pyridine	80	90-94
11	2-Bromoaniline	15	2,4-Dibromoaniline	75	78-80
12	2-Aminonaphthalene	5	2-Amino-1-bromonaphthalene	81	-

Table 2. Bromination of aromatic phenols using $La(NO_3)_3{\cdot}6H_2O$ at room temperature.

S. No	Substrate	Time (min)	Product	Yield (%)	Mp. (°C)
1	Phenol	5	4-Bromophenol	88	64-66
2	2-Methylphenol	10	4-Bromo-2-methylphenol	80	62-64
3	3-Methylphenol	28	4-Bromo-3-methylphenol	81	61-63
4	4-Methylphenol	13	2-Bromo-4-methylphenol	77	55-57
5	2-Hydroxy-benzaldehyde	42	4-bromo-2-hydroxybenzal-dehyde	74	-
6	2,6-Dimethyl-phenol	34	4-Bromo-2,6-dimethylphenol	80	76-79
7	4-Methoxy-phenol	22	2-Bromo-4-methoxyphenol	88	-
8	4-Hydroxy-3-methoxy-benzaldehyde	55	3-Bromo-4-hydroxy-5-methoxy-benzaldehyde	84	162-166
9	4-Nitrophenol	18	2-Bromo-4-nitrophenol	75	113-115
10	2-Naphthol	24	1-Bromo-2-naphthol	83	83-85
11	3-Methoxy-2-naphthol	17	1-Bromo-3-methoxy-2-naphthol	82	98-101

The method used cheaper catalyst $La(NO_3)_3{\cdot}6H_2O$ compared to other expensive transition metal catalyst and found to be effective against number of aniline and phenol derivatives with very good yields. The structure of brominated anilines and phenols were confirmed with NMR and mass spectroscopy and spectral data of some selected compounds is presented. The melting points of the products determined by capillary method are found in accordance with the literature ones.

Conclusion

In conclusion, we have presented a simple, efficient and economic methodology for mono-bromination of anilines and phenols using $La(NO_3)_3{\cdot}6H_2O$ as catalyst. The method is regioselective, offering potential in various synthetic applications giving up to 85% yield of the products. The protocol was successfully applied to number of aniline and phenol derivatives.

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