

**AN ECONOMICAL AND ECOFRIENDLY REGIOSELECTIVE BROMINATION OF  
ACETANILIDES USING POTASSIUM BROMIDE AND CERIC AMMONIUM  
NITRATE IN POLYETHYLENE GLYCOL**

**Ritu Gupta\* and Lata**

*Daulat Ram College, Department of Chemistry,  
University of Delhi, Delhi-110007, India  
E-mail: [ritu\\_chemistry12@yahoo.com](mailto:ritu_chemistry12@yahoo.com)*

**ABSTRACT**

A fast, economically, eco-friendly and highly chemo-regioselective method for the bromination of electron rich aromatic molecules has been developed by electrophilic substitution of Br<sup>+</sup>, which is generated in *situ* from KBr using ceric ammonium nitrate as the lewis acid catalyst in PEG-400 and the products are produced in highly excellent isolated yields and crude products do not require any further purification. Free aromatic amines remained unaffected under the reaction conditions.

**KEYWORDS**

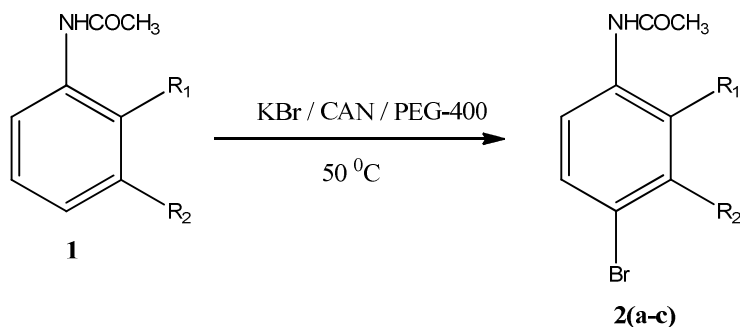
Chemo and regioselective, ceric ammonium nitrate (CAN), potassium bromide, polyethylene glycol (PEG).

**INTRODUCTION**

Halogenation is one of the most widely used and extensively studied aromatic substitution reaction<sup>1</sup> and similarly brominated arenes<sup>2</sup> are versatile intermediates for the synthesis of a wide variety of biologically active compounds. A large number of procedures have been reported for the direct bromination<sup>3</sup> in the literature but most of them are based on the use of direct liquor Br<sub>2</sub> i.e. toxic species, causes serious burns. So their uses create serious problems concerning their handling and disposal, especially in large scale and commercial applications. To neutralizing this problem, many methods of bromination of aromatic compounds have been developed including NBS-amberlyst,<sup>4</sup> KBr-H<sub>2</sub>O<sub>2</sub> using metal-oxo catalysts<sup>5</sup> and NBS-HZMS-5.<sup>6</sup> Now a days, KBr-*t*BuOBr-zeolite<sup>7</sup> and NaBO<sub>3</sub>·4H<sub>2</sub>O<sup>8</sup> are used as brominating agents. In spite of potential utility of some of these methods, they suffer from serious drawbacks, such as harsh reaction conditions, cumbersome extraction procedures, unsatisfactory yield, prolonged reaction time, usage of hazardous organic solvents and expensive catalysts. Thus, the development of a simple and efficient method under green protocol for the selective construction of these brominated arenes has been advocated. In this context, polyethylene glycol (PEG) is found to be an interesting solvent system.<sup>9</sup> It is a non-toxic, inexpensive, non-ionic liquid solvent of low volatility. PEG is a biologically acceptable polymer which has been used extensively in drug delivery and in

bioconjugates as tools for diagnostics<sup>10</sup>. Similarly, ceric (IV) ammonium nitrate (CAN) emerging as an important reagent for the synthesis of many compounds<sup>11</sup>. In addition, it has many advantages such as excellent solubility in water, cost-effectiveness, eco-friendly nature, easy handling, high reactivity, and make easy work-up procedures. Besides, CAN is able to catalyze various organic transformations not only based on its electron transfer capacity but also with its Lewis acidic property<sup>12</sup>. The environmentally benign nature of PEG and the versatility of CAN encouraged us to couple them together and study their utility in the synthesis of halogenated arenes. Exploring CAN as a powerful one-electron oxidant, we herein report for the first time a mild and efficient method for the bromination of activated aromatic compounds by using KBr as the bromine source, CAN as the Lewis catalyst and PEG as a greener solvent. As the electrophile Br<sup>+</sup> is generated *in situ* by the reaction of KBr and CAN, attacks the electron-rich aromatic rings. Surprisingly, free aromatic amines such as aniline did not respond at all. This is probably due to the formation of a salt of the free amine with the acidic CAN which makes the aromatic ring electron deficient.

In a typical reaction, a solution of CAN (1.3 mmol) and KBr (0.75 mmol) in PEG (15 mL) was added drop wise to a stirred mixture of arenes (0.5 mmol) in PEG (10 mL) at 50°C. After the addition was over, the reaction mixture was stirred for 10-15 minutes. It was poured over ice-cold water (20 mL) and white crystals appeared. The white crystals were filtered through Buchner funnel and the solid was dried. (**Scheme-I**)



**Scheme-I:** Arenes (0.5 mmol), CAN (1.3 mmol) and KBr (0.75 mmol) in PEG at 50°C.

Thus, a series of aromatic compounds was subjected to the bromination in presence of CAN and KBr in PEG-400 at 50°C, to furnish the corresponding bromo-arenes and the results are summarized in Table 1.

**Table 1.** Bromination of aromatic compounds by using CAN and KBr in PEG<sup>a</sup>

Entry (°C)	R <sub>1</sub>	R <sub>2</sub>	Time(min)	Yield <sup>b</sup> (%)	Mpt.	Lit
<b>2(a)</b> 171 <sup>13</sup>	H	H	15.0	89	169	170-
<b>2(b)</b> 158 <sup>14</sup>	CH <sub>3</sub>	H	10.0	92	158	156-
<b>2(c)</b> 104 <sup>15</sup>	H	CH <sub>3</sub>	10.0	90	103	103-

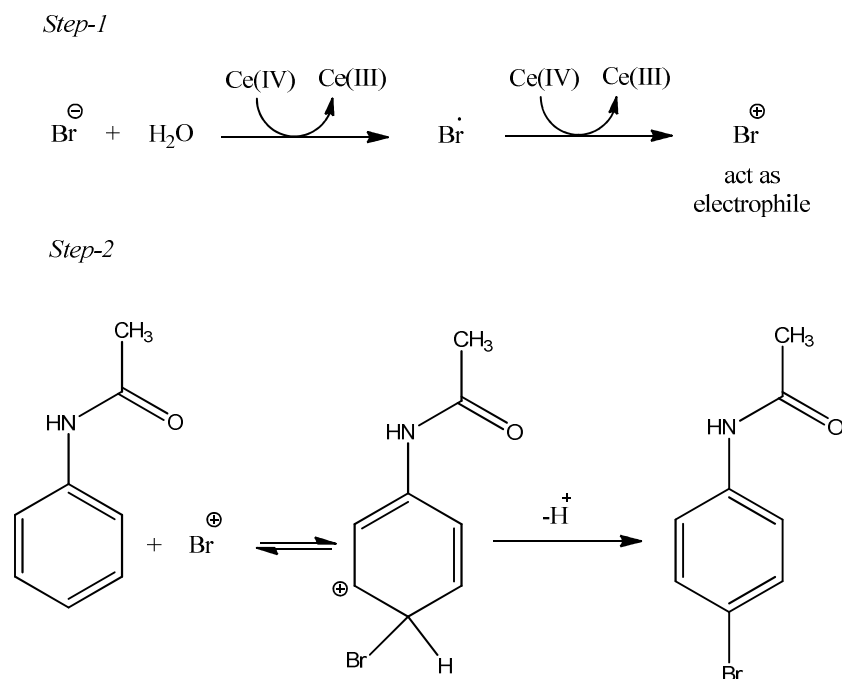
<sup>a</sup> Experimental detailed: Arenes (0.5 mmol), CAN (1.3 mmol) and KBr (0.75 mmol) in PEG at 50°C.

<sup>b</sup> Isolated yields.

**Note:** This procedure is general for aromatic compounds which substituted with electron donating groups.

### MECHANISM

As it is well understood that Ce<sup>4+</sup> is a stronger oxidizing agent ( $E^\circ \sim 1.61$  V vs. N.H.E.) than even Cl<sub>2</sub> ( $E^\circ \sim 1.36$  V) and in the redox reaction Ce(IV) is converted to Ce(III), a one-electron change, signaled by the lightening of the solution colour from orange to a pale yellow (providing that the reactant and respective product are not strongly coloured). In this reaction, two moles of CAN utilizes for the production of one mole of bromonium ions (Br<sup>+</sup>) (step-1) and then this Br<sup>+</sup> attacks the activated arenes at ortho/para position (step-2). The proposed plausible mechanism (**Scheme-II**) for reaction follows as:



## CONCLUSION

In conclusion we have developed for the first time an effective catalytic system PEG-400/CAN for the synthesis of bromo derivatives of acetanilide using KBr as brominating agent at 50°C. The methodology is simple, efficient, regioselective and environmentally friendly with simple work-up.

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