

Note

High atom efficient and environment-friendly preparation of herbicides bromoxynil and ioxynil

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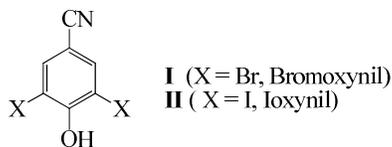
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High atom efficient and environment-friendly preparation of herbicides bromoxynil and ioxynil using bromide/bromate and iodide/iodate couple as halogenating reagent in water at room temperature is described.

Keywords: Bromide/bromate, atom efficient, herbicide, bromoxynil, ioxynil

The use of 3,5-dibromo-4-hydroxybenzonitrile (bromoxynil) **I** and 3,5-diiodo-4-hydroxybenzonitrile (ioxynil) **II** are well established as herbicides¹. Certain esters of bromoxynil, especially the octanoate, have been used extensively as herbicides in the control of broad-leafed weeds, particularly in crop growing areas². Although the esters have been shown to be highly effective, they have been produced only by incurring productivity penalties, which are aggravated by the expensive and cumbersome purifications that have till now been required.



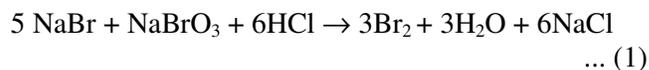
3,5- Dihalo-4-hydroxybenzonitrile

Bromoxynil and ioxynil were first synthesized by Auwers and Reis³ in 1896 by a complex four step procedure starting with 4-hydroxybenzaldehyde, an uneconomical method involving bromination, formation of the aldoxime, dehydration with concomitant acetate formation and hydrolytic removal of the acetate. Muller *et al.*⁴ has described a procedure for bromination of 4-hydroxybenzonitrile with elemental bromine in methanolic acetic acid. The product produced by the Muller process was

recovered by contacting the resulting bromination mixture with aqueous methanolic sodium hydrogen sulfite. Luckenbaugh *et al.*⁵ describes the production of bromoxynil or its sodium salt by carrying out bromination with elemental bromine in an aqueous suspension, especially aqueous caustic, followed by a chlorine spurge. Most of the reported methods for bromoxynil preparation involves the use of elemental bromine in their process^{6,7}. Despite the industrial importance of bromination process and the ever growing environmental concerns, the use of liquid bromine for bromination reaction is still very common in industry as well as in academia is probably due to its easy availability, low cost and lack of a better alternative. Moreover, purification of the reaction products is often demanding and laborious.

Results and Discussion

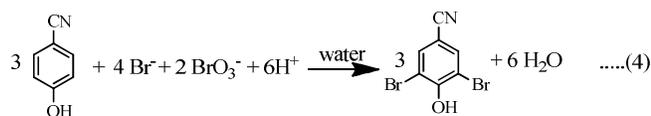
Recently we introduced a green brominating reagent utilizing the precursor of liquid bromine manufacture⁸. This precursor comprises a 5:1 mole ratio of NaBr-NaBrO₃ (designated as BR-A) which releases bromine on demand (*in-situ*) upon acidification (Eq. 1).



Alternatively, this reagent (BR-A) when treated with NaOCl furnished another reagent with a composition of 2:1 mole ratio of NaBr-NaBrO₃ (Eq. 2) (designated as BR-S) and used as such. This reagent (BR-S) releases BrOH on acidification (Eq. 3) and provides quantitative atom efficiency in aromatic



substitution and olefinic addition reactions which have been reported by us for few useful applications⁹. Our continuous efforts to achieve maximum bromide atom efficiency and minimize waste generation, as well as elimination of the use of hazardous liquid bromine and volatile organics led us to extend the utility of these reagents towards the preparation of extremely valuable herbicide bromoxynil (Eq 4)¹⁰.



Towards this end, we have focused our studies on the preparation of bromoxynil (**I**), as certain esters of bromoxynil are highly desirable and are shown to possess outstanding herbicidal properties¹⁻².

The main concern of the present work is particularly to develop an alternate method for the eco-friendly preparation of bromoxynil which obviates the drawbacks as detailed above. To our knowledge, no efficient methods for the synthesis of bromoxynil have been reported without use of liquid bromine. Herein, we report a highly efficient, technically pure and environment friendly method for the preparation of bromoxynil **I** from 4-hydroxybenzonitrile using NaBr/NaBrO₃ couple with a composition of equation 4 in aqueous acidic medium. Initially, various solvents were screened out for the preparation of bromoxynil **I** from 4-hydroxybenzonitrile with two equivalents of brominating reagent BR-S without any catalyst at room temperature (**Table I**). Quantitative yield of the product was obtained in all solvents studied. These results indicate the efficiency of the reagent independent of the solvent medium.

Due to the greenness of the process, we turned to the safer and universal solvent medium such as water (**Table I**, entry 6). The drawback of water as solvent in the present study is that, it requires 1:20 (w/v) ratio (substrate to water) to dissolve 4-hydroxybenzonitrile completely at room temperature. The amount of water could be reduced by conducting reaction at to 60°C on water bath, but, it has been observed that some complication due to occluded solid generation makes the reaction incomplete. However the process makes straightforward even by using 1:20 (w/v) substrate to water without compromising the yield and purity of the desired product. Present method does not pose any difficulties for the scaling up the reaction from lab scale 8.40 mmol to batch scale 1.26 moles under the optimized conditions (**Table I**, entry 8).

Thus, the present method has the following significant advantages from the standpoint of green chemistry: (i) high atom efficiency and no production of toxic waste materials¹¹, (ii) no catalyst is required at ambient reaction conditions, (iii) the use of water as a solvent, (iv) cheaper and easy availability of the reagents, (v) theoretically 100% conversions to

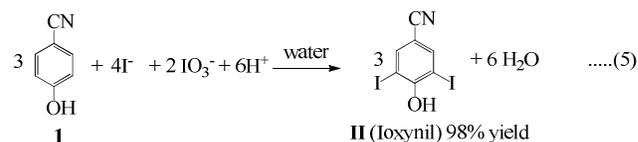
Table I — Optimization of reaction conditions for the preparation of bromoxynil (**I**)^a

Entry	Solvent	Time (hr)	Product yield (%)
1	CH ₂ Cl ₂	4.0	98
2	ClCH ₂ CH ₂ Cl	4.5	99
3	CH ₃ OH	4.0	98
4	EtOAc	6.0	99
5	CH ₃ CN	6.0	93
6	H ₂ O	4.5	98
7 ^b	H ₂ O	4.5	97
8 ^c	H ₂ O	4.5	98

^aReaction conditions: 4-hydroxybenzonitrile (1.0 g, 8.4 mmoles), H₂O (20 mL), NaBr (1.16 g, 11.26 mmoles), NaBrO₃ (0.85 g, 5.628 mmoles), 36% HCl (17.0 mmoles) unless otherwise stated. R. T. Product properly characterized by ¹H NMR, ¹³C NMR and melting points. ^b98% Sulfuric acid is used. ^cReaction carried out at 5 moles of substrate.

selective product, with no workup procedure only filtering and washing with water provides technically high pure product, (vi) finally eliminates the use of hazardous liquid bromine.

The preparation of ioxynil (**II**), using I/O₃⁻ as iodinating agent¹² under the optimized conditions described as in **Table I**, with high atom efficiency. Similar to bromoxynil, high yield and purity of ioxynil was obtained (Eq. 5). Both bromoxynil (**I**) and ioxynil (**II**) believed to possess high herbicidal activity than its chlo analogous^{1,2}. The use of sulfuric acid in place of hydrochloric acid in both cases **I** and **II** are verified with similar yields.



Experimental Section

General procedure for synthesis of bromoxynil (**I**)

4-Hydroxybenzonitrile **1** 1.0 g (8.40 mmoles) was dissolved in 20 mL of water placed in a 100 mL two-necked round bottomed flask with magnetic stir bar. To it an aqueous solution (20 mL) containing 1.16 g (11.26 mmoles) of sodium bromide and 0.85 g (5.628 mmoles) of sodium bromate was added and stirred for 30 min. To the above mixture 1.70 mL of 36% hydrochloric acid (0.017 mole) was added slowly under stirring at RT (30°C) over a period of 2 hr. The reaction-mixture was allowed to stir for another 2 hr.

The reaction-mixture was filtered through Buchner funnel, washed with deionized water (25.0 mL \times 2), the solid material was allowed to dry at 160 mm Hg pressure and then dried in oven at 80°C for 2 hr. The weight of the dried product 3,5-dibromo-4-hydroxybenzonitrile **I** was 2.265 g (97.0% yield), melting point observed 191°C. The products were confirmed by the comparison of their ^1H NMR, ^{13}C NMR, IR spectra and melting points with those of authenticated data⁷. Similar procedure was followed for the preparation of 3,5-diiodo-4-hydroxybenzonitrile using KI/KIO₃ as iodinating agent.

Conclusions

A highly efficient method for the synthesis of bromoxynil and ioxynil from 4-hydroxybenzonitrile, using bromide/bromate and iodide/iodate as halogenating agents with water as safe and eco-friendly solvent under ambient conditions precluding the use of hazardous liquid bromine, toxic reagents and harsh experimental conditions has been demonstrated. The reactions smoothly proceed in water offering high yield and purity of the desired products. The reagents used for the current transformation are inexpensively available in a common chemical laboratory. The simplicity, generality, and high atom-economy of this process make it attractive for the transformation of 4-hydroxybenzonitrile to bromoxynil and ioxynil both in small scale and large scale applications of commercial interest.

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- 11 Theoretically, only water and either NaCl or KCl are formed as by-products when NaBr/NaBrO₃ and KI/KIO₃ salts as halogenating reagents and hydrochloric acid is used in the reaction of Eq. 4 and 5 respectively.
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