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Regioselectivity in free radical bromination of unsymmetrical dimethylated pyridines

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ABSTRACT

During a literature review some curious inconsistencies in the free radical bromination of picolines were noted. To achieve a better understanding of the mechanisms and regioselectivity we reran these reactions, extending our work to unsymmetrical lutidines using N-bromosuccinimide in limiting amount. Characterization of the products was done with GC/MS and H NMR. The regioselectivity of bromination in unsymmetrical dimethylpyridines shows that nitrogen in the ring is deactivating inductively. The competition between 2,3, 2,4, and 2,5 dimethyl pyridine toward bromination results with bromination in the methyl group farthest from the N in the ring. 3,4-Lutidine shows only the 4,4-dibrominated product.

Introduction

N-bromosuccinimide (NBS) is one of the important brominating agents in organic synthetic chemistry. NBS is a convenient source of bromine for both free radical substitution[1] and electrophilic addition reactions.[2] NBS is economical, easy to handle, and easily available. The major advantage in the use of NBS is that the reaction byproduct (succinimide) can be easily removed.[3] NBS is a highly selective free radical brominating agent. NBS is widely used in radical bromination at allylic position of alkenes, known as Wohl–Ziegler bromination reaction.[3] Allylic bromination[4] can be obtained by refluxing the alkene solution and NBS in anhydrous carbon tetrachloride (CCl_4) using free radical initiator azobisisobutyronitrile (AIBN) or benzoyl peroxide (BPO). The formation of allylic bromides as the major product is due to the allylic radical intermediates formed during the course of the reaction which are much more stable than other carbon radicals.[4] When the same conditions as allylic bromination are applied to the benzylic bromination of aromatic compounds, NBS effects the bromination of benzylic positions.[5] Bromine can also be used for benzylic bromination[6] but many functional groups are sensitive to the generation of HBr during the reaction which competes with acid catalyzed bromination. This makes NBS the reagent of choice for bromination of polyfunctional aromatic compounds.

NBS is increasingly used for α-bromination of carbonyl compounds including indanone and cyclopentenone.[7] Various ketones and β-ketoesters are selectively α-brominated with NBS catalyzed by silica-supported sodium bicarbonate under free radical conditions.[3]

NBS is used as oxidant for an efficient enantioselective oxidation of secondary alcohols catalyzed by Mn(III)–salen complex.[8] NBS is also used as efficient catalyst in one pot synthesis of xanthane derivatives under solvent free condition[9] and polycyclic [2,3-*β*]quinolone derivative under ambient conditions.[10]

The reaction between methyl substituted anisole and NBS shows the competition between free radical bromination and electrophilic bromination. The competition can be carried out under conditions which favor the radical process, such as irradiation.[11] Competition between electrophilic aromatic and radical substitutions depends on the structures of electron-rich aromatic rings and the solvents used in the reactions.[12] The presence of methoxy group activates *p*-position of the aromatic ring and enhances nuclear bromination.[11] Electron donating groups in the benzene ring such as methoxy and acetanilide groups facilitate electrophilic ring substitution reaction.[13] The side chain bromination follows a radical pathway, while aromatic bromination is an electrophilic substitution reaction. Nuclear bromination is favored by a low temperature and polar solvents such as acetonitrile and dimethylformamide[14] while free radical bromination is favored by a high temperature and nonpolar solvents such as carbon tetrachloride and benzene.

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NBS bromination indicated that the bromine atom is the hydrogen abstracting species in all reactions.[15] Trace of bromine present in commercially available NBS may influence the stability of NBS.[16] The small amount of bromine radical produced by NBS with radical initiator BPO initiates the main propagation steps. NBS is a source of bromine, in low, steady state concentration and it consumes the liberated hydrogen bromide (HBr) by an ionic process.[17] The consumption of HBr avoids the inhibition of bromination.[18]

Free radical bromination with NBS was conventionally carried out using CCl_4 as solvent with various radical initiators.[2a] CCl_4 solvent is restricted due to its high toxicity, possible carcinogenicity, and ozone layer depleting effect.[19] Free radical benzylic brominations for several aromatic compounds are carried out in non-chlorinated solvents such as methyl formate and methyl acetate.[20] Free radical side chain bromination in supercritical carbon dioxide has shown similar selectivity to the conventional organic solvents.[21] Free radical bromination by NBS in pure water at ambient temperature and with visible light as initiator was conducted effectively. The aqueous phase permits easy isolation of the insoluble brominated product from water soluble succinimide byproduct. Aqueous NBS system is reported for selective benzylic bromination in the presence of ketone functionality.[13] However, water as solvent is limited for hydrophobic substrates only due to the poor solubility of most of organic compounds in water.[22] Benzylic bromination was achieved using (trifluoromethyl) benzene as solvent. (Trifluoromethyl)benzene is chemically inert and less toxic than conventional solvent CCl_4.[23]

The goal of our research work is to determine the reactive site and products of unsymmetrical dimethylpyridine and to achieve better understanding of the regioselectivity of the compound toward free radical NBS bromination (10%) and with stoichiometric amounts. NBS bromination of the unsymmetrical dimethyl pyridine was carried out with limiting NBS. Mono brominated product was initially obtained by using 10% of the reagent to find the reactive site of the compound. Reaction is further carried out in 1:1 equivalent to obtain a sufficient amount of monobrominated product so that it can be isolated and analyzed with the help of GC/MS, ^{1}H NMR, and NOE studies. Specifically, 2,3-, 2,5-, 2,4- and 3,4-dimethylpyridine were treated with NBS using the standard methods described in the Experimental section and the data were obtained and discussed. Since our research focus is to accomplish the understanding of regioselectivity toward NBS bromination of unsymmetrical dimethyl pyridine so no effort was taken to isolate and analyze the polybrominated products.

An unusual orienting effect in the bromination of alkyl bromides

The directive influence of polar substituents on free radical halogenation reaction has been studied by several groups.[24] The results agree with theory that the electronegative attacking radicals prefer position of higher electron density. The halogenation of several alkyl and cycloalkyl halides is through photo-bromination of alkyl bromides which is quite different from the bromination of other alkyl halides and from alkyl halide halogenations in general.[25] The chlorination of alkyl bromides is reported to produce the expected isomer distribution; preferential attack occurring at positions remote from the bromine substituent.

Electronic effect in selectivity σ^+ values for different positions of pyridine

The application of the Hammett equation for the prediction of the effects of substituents on the heterocyclic compounds was reported.[26] The derived σ^+ values have proven useful in correlating on electrophilic aromatic substitution and electrophilic side-chain reaction.[27]

Free radical bromination of toluene with different brominating agents was carried out. The rates relative to toluene for hydrogen abstraction from substituted toluene by various brominating agents were accumulated and an average ρ value of -1.42 was obtained nearly independent of the brominating agents. In all cases, an excellent fit of the points to the Hammett correlation was obtained when σ^+ values were used.[28]

Applying this work to picolines, σ values of 2-picoline and 4-picoline show that the reactivities of 2-picoline and 4-picoline should be similar whereas the reactivity of 3-picoline seems higher compared to 2 and 4-picolines owing to the higher σ value.[28] The order of reactivity of picoline comparing its σ value can be given as 3-methyl > 2-methyl > 4-methyl.

The reaction of 2-picoline with NBS to give a mixture of mono and di-substituted products was reported. Similarly 4-picoline was reacted with NBS and the product was isolated as the hydrobromide salt and was analyzed as fully brominated, that is; 4-tribromomethyl-pyridine. Kutney group reported that no brominated product was obtained with 3-methylpyridine under the same conditions. Their results conclude that in the methylpyridine series, the rate of reactivity toward NBS is 4-methyl > 2-methyl > 3-methyl.[29] The classical approach to explain reactivity in relation to σ value seems inadequate (Fig. 1).

Result and discussion

The bromination of 2-methyl pyridine and 3-methylpyridine was carried out in 1:1 stoichiometry for 24 h. The bromination at the methyl branch to give 2-Bromomethylpyridine and 3-Bromomethylpyridine was reported. However the yield is low. 3-Bromomethylpyridine is a known compound. It was prepared from 3-aminomethylpyridine. 2-Bromomethyl pyridine is also a known compound. It is prepared either directly from 2-picoline by NBS bromination or from pyridin-2-ylmethanol (Scheme 1).

The classical approach to predict the substituent effect on the reactivity of the free radical bromination of picolines by NBS is not adequate. Hence, we revisited in this article the reactions to investigate the reactivities of 2, 3, and 4-picolines toward the free radical bromination by NBS and extended the work to symmetrical and unsymmetrical lutidines as well (Scheme 2).

Free radical bromination of 4-methylpyridine gives only dibrominated product that can be explained as in case of 3,4-dimethylpyridine as above. In the case of 3-methylpyridine bromination at methyl group does not take place instead ring substituted product was obtained as shown in Table 2 (entry 6b) probably by non radical mechanism. It is not clear why 3-methyl group in 3-methylpyridine is not brominated. The unsuccessful attempt of bromination of 3-methylpyridine was reported.[31] The unusual nuclear bromination in the presence of side chain in aromatic compounds under apparent radical conditions was reported in the literature.[11,32] The reaction of 3,5-dimethylanisole with NBS under irradiation did not yield the expected side chain substituted product instead a nuclear brominated product, that is; 4-bromo-3-(bromomethyl)-5-methylanisole was obtained.[11] The reaction of 3-methyl pyridine with NBS under free radical reaction conditions belongs to this category.

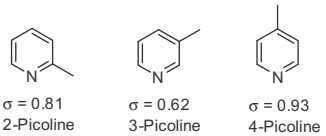

Figure 1. σ-Value of picolines.