REGIOCONTROLLED NITRATION OF 4-QUINOLONES AT AMBIENT CONDITIONS

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GRAPHICAL ABSTRACT

Abstract Regiocontrolled nitration of 4-quinolone, the highly privileged scaffold, has been developed at ambient conditions. The nitro group can selectively be introduced at diverse positions simply by tuning the reactivity of the moiety. Discrimination is being achieved through the selective functionalization of the free N-H group. The functional group has been screened theoretically with the help of Fukui function and local softness calculation. Theoretical predictions are synchronized well with the experimental findings. Finally, this nitration technique allows quick access to the structurally diverse 4-quinolones.

Keywords Ambient conditions; Fukui function; local softness; 4-quinolones; regiocontrolled nitration

INTRODUCTION

Nitration has been extensively studied since its discovery in 1834.[1] Nitro compounds are significantly beneficial synthetic intermediates and have potential application in various fields, especially in the chemical industry and pharmaceuticals.[2] A variety of aromatic nitro compounds are used for the treatment of insomnia, angina, Parkinson, and trypanosomatid diseases.[2b] Various methodologies have been employed to synthesize the aromatic nitro compounds. Nitrination using mixed acids is most widely used technique and results in a mixture of products. Afterward, many regioselective nitration techniques such as ipso-nitration/oxidation of amine[3]
or azide, functional group directed nitration, etc., have been developed to overcome those shortcomings. However, these modern and sophisticated techniques are not always helpful for designing target molecules.

In the arena of 4-quinolones, multisubstituted 4-quinolones are prominent in bioactive molecules and their selective functionalization remains a challenge. Our main effort was directed toward the regioselective functionalization of 4-quinolones. Slight variation in the substituent nature or position (Fig. 1) greatly varies the potency of the quinolone-based drugs.

Nitro-quinolone derivatives have been reported to possess antifilarial, antiviral, antiallergic, antitumor, and antibacterial capabilities. So far, very limited and mostly 6-nitro derivatives of 4-quinolones have been synthesized and their medicinal values evaluated. This might be due to the problems associated with common synthetic methodologies, as these include the cyclization of nitro-substituted anilines to form the desired nitro-quinolone. It is difficult to use the literature method if one aims to get 5- or 7-nitro 4-quinolone because the starting unsymmetrical nitro anilines upon cyclization always result in the formation of mixture products (isomers), in turn leading to cumbersome separation process as well as poor yield. No such direct technique for the selective nitration of 4-quinolone has been reported in the literature. Selectivity in the nitration reaction is governed by various factors such as steric effects, nature of solvent, and interaction between substrate with reagents and electronic effects. Under the identical reaction conditions, regioselectivity is governed by the electronic effects of the substrate.

Herein for the first time, we report a complete regiocontrolled nitration of 4-quinolones at ambient conditions. Selectivity can easily be tuned by the selective functionalization of free N-H group of 4-quinolone. The profound impacts of the free N-H and other substituents in the nitration process of 4-quinolones have been screened with the help of density functional theory (DFT) calculation using a synchronized study based on theoretical prediction and experimental observations.

RESULTS AND DISCUSSION

Our study began with the nitration of 4-quinolone 3-carboxylate using mixed acids at ambient conditions. The unsubstituted 4-quinolone 3-carboxylate 1 has been selected as a model compound for this study. There are five positions (C-2, C-5, C-6, C-7, and C-8) available for nitration. Compound 1 on nitration with mixed acids at
ambient conditions results in 78% yield of the corresponding 5-nitro derivative upon isolation (Table 1). Carrying out the reaction in the presence of both dilute and concentrated nitric acid did not provide any good result (Table 1). During the modification of reaction conditions, keeping the presence of the acid-sensitive group in mind, we focused on developing the nitration reaction in neutral conditions. Various sets of well-known nitrating reagents were used and corresponding results are summarized in Table 1. It is clear from the table that the combination of nitronium tetrafluoroborate [NTFB] and acetonitrile (Table 1, entry 6) is best suited in the present study, which results in 90% yield of the desired product within 5 min at ambient conditions. Nitration using NTFB generally proceeds via Eq. (1).[11]

\[ \text{ArH} + \text{NO}_2^+\text{BF}_4^- \rightarrow \text{ArNO}_2 + \text{HF} + \text{BF}_3 \]

With the optimized conditions in our hand, the scope of selective nitration was investigated (Scheme 1). Different substituted 4-quinolones 2 and 3 smoothly underwent selective nitration to furnish the desired 5-nitro product in excellent yield. The results clearly showed that the presence of an electron-donating group (-CH₃) and electron-withdrawing group (-F) has no significant role in defining the position of incoming electrophile (nitronium group).

The problem begins while attempting the nitration of compound 4, which has a methoxy group present at the C-8 position. Compound 4 on nitration under the optimized conditions always results in the corresponding 5,7-dinitro derivatives (Scheme 2). This is probably due to the +R effect of methoxy group, which facilitated the second nitration in its ortho-position.

This observation made us develop a regioselective nitration technique. To control the nitration reaction we thought to tune the reactivity of compound 4. Accordingly, an additional functional group has been introduced (functionalization of free N-H) into the moiety so that it could trim down the reactivity of the parent

Table 1. Optimization of the reaction conditions

| No. | Reagent(s)-Solvent     | Time | Temperature | Yield (%)<sup>a</sup> |
|-----|------------------------|------|-------------|----------------------|
| 1   | Mixed acids            | 1 h  | 0 °C rt     | 78                   |
| 2   | HNO₃ (dil.)            | 2 h  | rt          | 30                   |
| 3   | HNO₃ (conc.)           | 2 h  | rt          | 52                   |
| 4   | Cu(NO₃)₂, p-TSA-DCM    | 12 h | rt          | No reaction         |
| 5   | Fe(NO₃)₃, Ac₂O-DCM     | 12 h | rt          | No reaction         |
| 6   | NTFB                   | 5 min| rt          | 90                   |

<sup>a</sup>Isolated yield after column chromatography purification.
compound 4 and thereby restrict the second nitration. Selection of the functional group has been done with the help of B3LYP density functional theory (DFT) calculation using the Gaussian 03 W quantum chemical package. Among the different density functionals, the hybrid functional B3LYP is by far the most popular in chemistry. It is well documented that the B3LYP functional along with 6-31G(D) or 6-31G(D,P) basis function can be used in studying various organic reactions. Here we have chosen the 6-31G(D,P) basis function for our computation. Regioselectivity as well as reactivity of any molecule can be ascertained through evaluation of Fukui function and local softness. The Fukui function \( f_i^k \), instigated in density functional theory (DFT) by Parr and Yang, is the most important local reactivity index. For electrophilic attack it is defined as \( f_i^k = \rho_k(N) - \rho_k(N - 1) \), where \( \rho(N) \) and \( \rho(N - 1) \) are the electron densities of the N and (N - 1) electron systems respectively. Local softness \( s_k \) is another parameter in analyzing the regioselectivity, which is related to Fukui function as \( s_k = f_i^k \) with \( i = + \) or \( - \), where \( S \) is the global softness given as \( S = 1/2\eta \), where \( \eta \) is the global hardness.

The detail results of the nucleophilic Fukui function \( f_i^k \) and local softness \( s_k \) calculation are shown in Tables 2 and S-I (see supporting information). It is clear from theoretical analysis that either an alkylester or -CH2Ph group can be chosen for the functionalization of free N-H to restrict the second nitration. Herein, we have selected the alkylester group as the resulting moiety 5 can serve as an amino acid precursor. Nitration of compound 5 under the optimized condition selectively results in the corresponding 5-nitroderivative in excellent yield upon isolation (Scheme 3).

Now the remaining major challenge is the introduction of nitro group selectively at the 7-position of the same moiety (compound 4). After screening several protecting groups with the help of conceptual DFT, we found -SO2CF3 may be chosen in this case (Table 2). As for -SO2CF3 N-protecting group C7 is susceptible for electrophilic attack, having greater reactivity indices \( f_i^k = 0.027, s_k = 0.158 \) than the other
probable sites C5 (0.020, 0.120) and C6 (0.015, 0.091). Accordingly, the parent compound 4 on treatment with triflic anhydride in the presence of tetrabutyl ammonium hydrogen sulfate (TBAHS) results in the desired N-protected 4-quinolone 6 in good yield. The protected quinolone (6) on nitration under the optimized conditions results in the corresponding mono nitro-derivative after in situ deprotection. The 7-nitro derivative of compound 6 has been isolated selectively in moderate yield (Scheme 4).

This study showed that the N-H group plays a pivotal role in defining the position of the nitro group in the nitration reaction of 4-quinolone moieties. Tuning of the reactivity in the nitration reaction was further justified using another model compound 7 where the methyl group is present in the C-6 position. The DFT calculation of compound 7 showed that the most reactive position for the electrophilic attack is C-8, as it has greater reactivity index ($f_k = 0.042, s_k = 0.240$) than the other possible sites (C-5 and C-7, Table 2).

Functionalization of free N-H either with alkylester or $-\text{SO}_2\text{CF}_3$ changes the reactivity and C-5 becomes the most susceptible position for the attack of nitronium ion (Tables 2 and S-I). Among alkylester and $-\text{SO}_2\text{CF}_3$, the former has greater reactivity indices and accordingly, the free N-H of compound 7 was protected with alkylester (compound 8) following the previous method (compound 5). Both the compounds 7 and 8 were subjected to the nitration reaction in our optimized conditions and resulted in the corresponding 8 and 5 nitro derivatives in 80 and 82% yields respectively.

| Compound | Fukui functions | Local softness | Theoretically preferred reaction center | Experimentally preferred reaction center |
|----------|-----------------|----------------|----------------------------------------|----------------------------------------|
| 1        | 0.043 0.030 0.015 — | 0.248 0.173 0.085 — | C-5 | C-5 |
| 2        | 0.038 0.027 0.020 — | 0.220 0.156 0.113 — | C-5 | C-5 |
| 3        | 0.042 0.027 0.020 — | 0.238 0.150 0.111 — | C-5 | C-5 |
| 4        | 0.037 0.025 0.027 — | 0.217 0.145 0.156 — | C-5 | C-5 and C-7 |
| 5        | 0.033 0.027 0.019 — | 0.193 0.160 0.113 — | C-5 | C-5 |
| 6        | 0.020 0.015 0.027 — | 0.120 0.091 0.158 — | C-7 | C-7 |
| 7        | 0.041 — 0.018 0.042 | 0.238 — 0.105 0.240 | C-8 | C-8 |
| 8        | 0.038 — 0.015 0.037 | 0.220 — 0.088 0.218 | C-5 | C-5 |

Scheme 3. Controlled nitration of compound 5.
CONCLUSION

Finally, the newly developed technique allows introducing the nitro group in diverse positions of the 4-quinolone ring with maximum efficiency. This method would be very useful for the target synthesis of new bioactive molecules based on a 4-quinolone system. The study showed that the N-H functional group plays a pivotal role in defining the position of incoming electrophile. Judicial functionalization of free N-H brings the discrimination and allows selective nitration of 4-quinolones. Other part of the development based on this moiety is currently under way.

EXPERIMENTAL

Unless stated otherwise, all reagents such as o-anisidine, p-toluidine, aniline, o-F-aniline, o-toluidine, diethylethoxy methylene malonate (EMME), potassium carbonate, tetrabutylammoniumhydrogensulfate (TBAHS), nitronium tetrafluoroborate (NTFB), (CF₃SO₂)O and solvents were used as received from commercial suppliers. NMR spectra were recorded on a 300-MHz spectrometer at 298 K and calibrations were done on the basis of solvent residual peak. Mass spectra were performed using ion trap mode. Products were purified using column chromatography on silica gel.
(60–120 mesh) and a mixture of petroleum ether (60–80 °C)/ethyl acetate was used as an eluent. Progress of reaction was monitored by silica-gel thin-layer chromatography (TLC).

Preparation of Compounds 1–4[6]

A mixture of aniline (10 mmol), EMME (11 mmol), and toluene (30 mL) was refluxed in a 250-ml round-bottom flask for 5 h. It was then cooled and washed with 3 (N) 100 mL H2SO4. Toluene was distilled off afterward. The mixture was scratched vigorously to get solid anil product. This product (5 g) was refluxed with biphenyl-oxide (50 mL) for 2 h at 280 °C. It was then cooled and stirred for an hour after addition of a small amount (100 mL) of petroleum ether. Compounds 1–4 were obtained by filtration on Buchner funnel.

General Procedure of Nitration Reaction (Compounds 1a–8h)

A mixture 4-quinolone-3-carboxylate (1 mmol) in 5 ml dry acetonitrile was taken in a 25-ml round-bottom flask. Then, 2 mmol (0.266 g) of NTFB (nitronium tetrafluroborate) was added into it at a time. The reaction mixture was stirred at room temperature for 5 min. The progress of reaction was monitored by TLC, and upon completion the reaction mixture was poured into the ice water and a yellow solid appeared. The yellow solid material was collected and dried completely. The crude material was further purified by the silica-gel column chromatography using ethyl acetate and petroleum ether as an eluent.

Ethyl 1,4-Dihydro-8-methoxy-5,7-dinitro-4-oxoquinoline-3-carboxylate (4d)

Bright yellow solid, melting point 175–178 °C; 1H NMR (DMSO-d6, 300 MHz) δ 1.27 (t, J = 7.2 Hz, 3H), 4.12 (s, 3H), 4.23 (q, J = 7.2 Hz, 2H), 8.37 (s, 1H), 8.49 (s, 1H); 13C NMR (DMSO-d6, 75 MHz) δ 14.66, 60.75, 64.38, 113.25, 114.83, 121.48, 136.79, 142.12, 143.54, 146.13, 146.30, 164.18, 170.26. HRMS (ESI-TOF) m/z: [M + H]+, found 338.0522. C13H11N3O8 requires 338.0624.

FUNDING

We thank the Department of Science and Technology (DST), New Delhi, for financial support (SR/FT/CS-017/2010). P. G is grateful to the University Grants Commission for the award of a fellowship.

SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher’s website.

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