Anal. Calcd for $C_{21}H_{21}FClNO_2$: C, 67.47; H, 5.66 N, 3.75; Cl, 9.48. Found: C, 67.38; H, 5.73; N, 3.72; Cl, 9.40.

3f: R^1 = H, R^2 = H, R^3 = *t*-Bu; mp 104-105 °C (lit.[16] mp 102-104 °C); ^{1}H NMR ($CDCl_3$) δ 1.01 (s, 9 H, CMe_3), 2.63 (s, 2 H, CH_2), 6.25 (d, J = 2.1 Hz, 1 H, H-3), 7.1-7.6 (m, 4 H, aromatic), 7.8 (br s, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 29.7, 31.9, 43.0, 101.9, 110.4, 119.6, 119.8, 121.0, 128.9, 135.7, 137.6.

3g: R^1 = H, R^2 = H, R^3 = *i*-Pr; mp 42-43 °C (lit.[17] mp 42.5 °C); ^{1}H NMR ($CDCl_3$) δ 1.01 (d, 6 H, Me_2CH), 2.01 (m, 1 H, $CHMe_2$), 2.64 (d, 2 H, CH_2), 6.28 (s, 1 H, H-3), 7.12 (m, 2 H), 7.32 (m, 1 H), 7.57 (d, 1 H), 7.83 (br s, 1 H, NH).

3h: R^1 = H, R^2 = H, R^3 = Me; ^{1}H NMR ($CDCl_3$) δ 1.39 (t, 3 H, CH_2CH_3), 2.82 (q, 2 H, CH_2CH_3), 6.28 (s, 1 H, H-3), 7.1-7.6 (m, 4 H, aromatic), 7.85 (br s, 1 H, NH). NMR matches that reported previously.[7]

3i: R^1 = H, R^2 = Me, R^3 = Et; mp 41.5-42.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.11 (t, 3 H, CH_3CH_2), 1.81 (m, 2 H, $CH_2CH_2CH_3$), 2.77 (t, 2 H, $CH_2CH_2CH_3$), 3.71 (s, 3 H, NMe), 6.31 (s, 1 H, 3-H), 7.20 (m, 3 H), 7.59 (d, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.0, 21.9, 28.9, 29.4, 98.7, 108.7, 119.2, 119.7, 120.5, 127.9, 137.5, 142.0.

3j: R^1 = H, R^2 = Me, R^3 = *i*-Pr; ^{1}H NMR ($CDCl_3$) δ 1.11 (d, 6 H, J = 6.5 Hz, Me_2CH), 2.10 (m, 1 H, $CHMe_2$), 2.72 (d, 2 H, J = 7.2 Hz, CH_2), 3.74 (s, 3 H, NMe), 6.37 (s, 1 H, H-3), 7.16-7.39 (m, 3 H, aromatic), 7.68 (d, 1 H, aromatic); ^{13}C NMR ($CDCl_3$) δ 22.7 (q), 28.4 (d), 29.6 (q), 36.2 (t), 100.0 (d), 108.9 (d), 119.3 (d), 119.8 (d), 120.5 (d), 128.0 (s), 137.4 (s), 140.4 (s).

2a: R^1 = 2-quinolylmethoxy, R^2 = 4-$ClC_6H_4CH_2$, R^3 = Me; ^{1}H NMR ($CDCl_3$) δ 2.22 (s, 3 H, CH_3), 2.25 (s, 3 H, CH_3), 5.22 (s, 2 H, CH_2N), 5.46 (s, 2 H, CH_2O), 6.8-8.2 (m, 13 H, aromatic).

2c: R^1 = 2-quinolylmethoxy, R^2 = 4-$ClC_6H_4CH_2$, R^3 = CH_2CO_2Et; ^{1}H NMR ($CDCl_3$) δ 1.21 (t, 3 H, J = 7.5 Hz, CH_2CH_3), 2.32 (s, 3 H, CH_3C), 3.69 (s, 2 H, CH_2COOR), 4.11 (q, 2 H, J = 7.5 Hz, CH_2CH_3), 5.23 (s, 2 H, CH_2N), 5.47 (s, 2 H, CH_2O), 6.8-8.3 (m, 13 H, aromatic); ^{13}C NMR ($CDCl_3$) δ 10.4 (q), 14.2 (q), 30.6 (t), 46.0 (t), 60.7 (t), 71.8 (t), 102.2 (d), 104.7 (s), 109.7 (d), 111.2 (d), 119.2 (d), 126.3 (d), 127.3 (d), 127.5 (s), 127.6 (d), 128.3 (s), 128.85 (d), 128.87 (d), 129.6 (d), 131.7 (s), 133.0 (s), 135.0 (s), 136.3 (s), 136.8 (d), 147.5 (s), 153.0 (s), 158.7 (s), 171.8 (s).

2e: R^1 = F, R^2 = 4-$ClC_6H_4CH_2$, R^3 = $C(Me)_2CO_2Me$; mp 116-117 °C; ^{1}H NMR ($CDCl_3$) δ 1.78 (s, 6 H, CMe_2), 2.28 (s, 3 H, 2-Me), 3.70 (s, 3 H, CO_2Me), 5.24 (s, 2 H, CH_2N), 6.85 (m, 3 H), 7.06 (dd, 1 H), 7.26 (m, 2 H), 7.39 (q, 1 H); ^{13}C NMR ($CDCl_3$) δ 11.7 (q), 27.5 (q), 43.8 (s), 45.8 (t), 52.3 (q), 105.2 (d, J_{CF} = 24.7 Hz), 108.9 d, J_{CF} = 26.3 Hz), 109.6 (d, J_{CF} = 19.8 Hz), 127.1 (d), 129.0 (d), 132.9 (s), 133.2 (s), 133.8 (s), 136.0 (s), 157.7 (s, J_{CF} = 233 Hz), 178.5 (s). Anal. Calcd for $C_{21}H_{21}FClNO_2$: C, 67.47; H, 5.66; N, 3.75; Cl, 9.48. Found: C, 67.43; H, 5.70; N, 3.71; Cl, 9.45.

2i: R^1 = H, R^2 = Me, R^3 = Et; ^{1}H NMR ($CDCl_3$) δ 1.33 (t, 3 H, CH_2CH_3), 2.45 (s, 3 H, CH_3C), 2.87 (q, 2 H, CH_2CH_3), 3.71 (s, 3 H, NCH_3), 7.28 (m, 3 H), 7.64 (d, 1 H).

Supplementary Material Available: NMR spectra for compounds **4**, **1a-c**, **1f-j**, **3i**, **3j**, **2a**, **2c** and **2i** (19 pages). Ordering information is given on any current masthead page.

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Aprotic Nitration ($NO_2^+BF_4^-$) of 2-Halo- and 2,6-Dihalopyridines and Transfer-Nitration Chemistry of Their *N*-Nitropyridinium Cations

Joseph L. Duffy† and Kenneth Khosrow Laali*

Department of Chemistry, Kent State University, Kent, Ohio 44242

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$NO_2^+BF_4^-$ nitration of 2,6-dibromo-1 and 2,6-dichloropyridine **2** in CH_3CN results in predominant C-nitration, whereas in CH_2Cl_2, N-nitration is predominant. With 2,6-difluoropyridine **3** only C-nitration was observed. Dehalogenation of the C-nitrated **1** and **2** affords 3-nitropyridine (3-NP) in moderate but greatly improved yields over conventional protic nitration of pyridine. Despite favorable presence of steric inhibition to resonance and the $-I$ effect of halogens, N-nitrated pyridinium salts **1b** and **2b** do not transfer-nitrate to aromatics even under forcing conditions. The lack of transfer-nitration reactivity is not due to in situ rearrangement of the nitro onium to nitrito onium ions. A mechanism involving neighboring group participation by the 2,6-halogens is proposed. The monohalo-*N*-nitropyridinium cations transfer-nitrate toluene and benzene. Transfer-nitration selectivity of the 2-bromo-*N*-nitro- and 2-chloro-*N*-nitropyridinium cations are comparable (K_T/K_B = 41-44), but the 2-fluoro-*N*-nitro cation is much less selective (more reactive) (K_T/K_B = 15.4), indicative of a stronger $-I$ effect, weakening the N^+-N^+ bond.

Introduction

C-Nitrated pyridines and their derivatives are important intermediates in syntheses of heterocyclic compounds and in dyes and pharmaceutical products.[1] Whereas 4-nitropyridine (4-NP) is obtained in high yields (90%) by nitration of the *N*-oxide and subsequent reduction, 3-nitropyridine (3-NP) was obtained only in low yields (5%) under forcing condition (HNO_3/H_2SO_4; 370 °C).[2]

An indirect route to 3-NP involving selective oxidation of 3-aminopyridine is available, but electrophilic nitration in reasonable yields was not achieved. Although application of 2,6-di-*tert*-butyl blocking groups leads to exclusive C-nitration, deblocking (transalkylation) proved impossible even in superacids, as facile N-protonation prevents the formation of a high-energy ipso protonated dication intermediate.[3]

We report herein our aprotic nitration studies utilizing dihalo blocking groups. Our rational was that (a) presence of bulky halogens should reduce N-nitration both sterically and inductively; (b) C-nitration at position 3 should be

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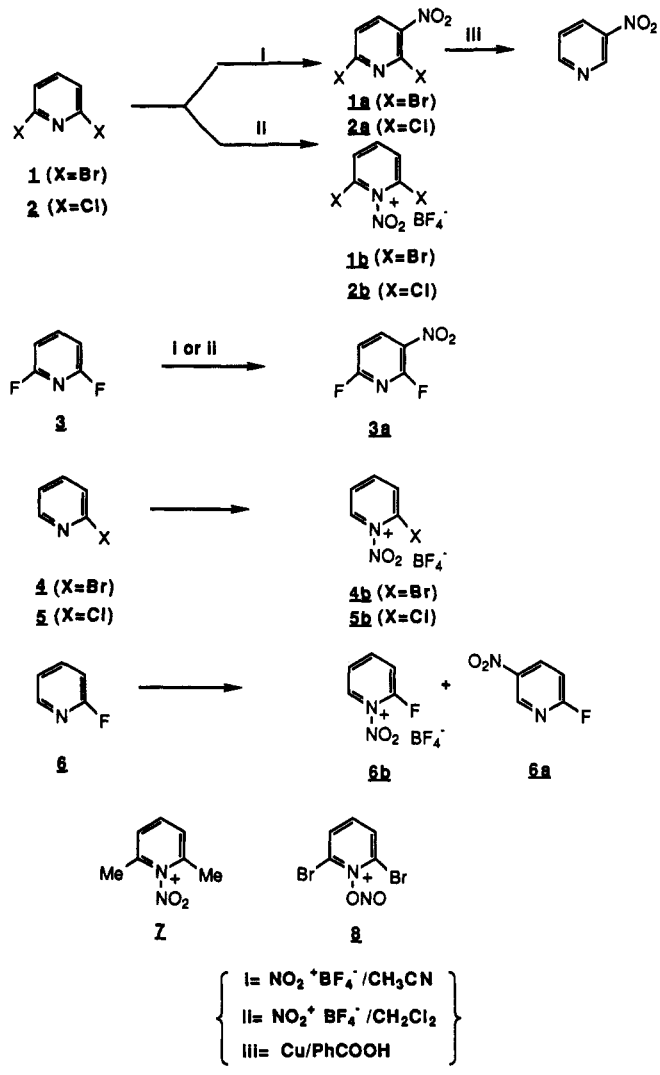
Scheme I. N- and C-Nitration of 2,6-Dihalo- and 2-Halopyridines



favored by p-π back-bonding; and (c) dehalogenation of the nitrodihalopyridine should be feasible.

Results and Discussion

Nitration of **1** and **2** in excess (2 equiv) $NO_2^+BF_4^-$ in refluxing CH_3CN (homogeneous nitration) gave 70–80% yield (GC) of the *C*-nitro products **1a** and **2a** (Scheme I).[4] In refluxing methylene chloride (heterogeneous nitration) and with excess substrate, the *N*-nitropyridinium tetrafluoroborates **1b** and **2b** precipitated and were isolated as moisture-sensitive white crystalline solids. Minor amounts of the *C*-nitro products were also formed (40–50%).

The observed solvent dependency of regioselectivity suggests the differing nature of the nitration electrophile. Preferred C-nitration in CH_3CN may be explained by complexation with solvent (N-nitration of solvent) and subsequent transfer-nitration to 2,6-dihalopyridine. As the NO_2–CH_3CN complex is sterically more demanding, N-nitration is inhibited.

In control experiments, **1b** did not transfer-nitrate to excess **1** to give **1a**. Similarly, **1b** could not be C-nitrated with excess $NO_2^+BF_4^-$ to give **1a** upon workup. Thus, N- and C-nitrations must occur independently. In another control experiment, isolated **1a** was allowed to react with $NO_2^+BF_4^-$ in refluxing CH_3CN. GC analysis indicated no dinitration to give 3,5-DNP.

Nitration of **3** under the conditions favoring N-nitration (CH_2Cl_2) led only to C-nitration (Scheme I). This illustrates both a better *I* effect and a more facile p-π interaction imposed by the 2,6-fluorines. The less crowded monohalopyridines **4** and **5** could only be N-nitrated (**4b**, **5b**) irrespective of solvent and mode of nitration. With **6**, whereas N-nitration was predominant (**6b**), C-nitration was also observed as a minor pathway to give 2-fluoro-5-nitropyridine, **6a** (6%).

The C-nitrated products **1a** and **2a** were dehalogenated with copper in hot benzoic acid[5] to give 3-NP in 23% and 37% isolated yields, respectively. Attempted reduction with copper in refluxing TFA led to partial dehalogenation in low yields. Similarly, whereas **1** itself was quantitatively converted to pyridine by reductive dehalogenation with $(Bu)_3SnH$, with the mononitro product **1a**, only one halogen was removed even under forcing conditions in excess reducing agent.

Thus $NO_2^+BF_4^-$ nitration in CH_3CN and subsequent dehalogenation provides convenient access to 3-NP through an electrophilic route.

Transfer-Nitration Chemistry. *N*-Nitropyridinium salts are effective transfer-nitrating agents for aromatics (Scheme II).[6] The reactions are characterized by high substrate selectivity (K_T/K_B = 36.5–44.5) and a well defined regioselectivity (ortho/para = 1.85–1.94) in competitive nitrations. Presence of methyl group(s) in the 2-(quinolinium) and 2,6-positions (lutidinium) increases reactivity by steric inhibition to resonance which reduces the contribution of the resonance structures involving $N^+{=}N^+$.

With pyridinium salts **1b** and **2b** not only steric inhibition to resonance but also the *–I* effect of halogens should further weaken the N–N bond. We expected, therefore, **1b** and **2b** to be reactive transfer-nitrating agents for aromatic nitration under acid-free conditions. However, in repeated experiments, no transfer-nitration could be observed with benzene/toluene mixtures even under reflux, and the onium ions were isolated intact from the reaction mixture (NMR). On the other hand, the monohalo-

Scheme II. Transfer-Nitration to Aromatics

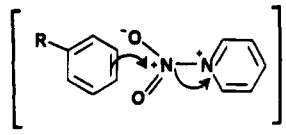


Table I. Substrate (k_T/k_B)[a] and Positional Selectivity (Isomer Distribution) in Transfer-Nitration with Substituted *N*-Nitropyridinium Salts

		isomer distribution (%)			
substituent(s)	k_T/k_B	ortho	meta	para	o/p
2,6-Me_2	35.1	65	3	32	2.03
2-Br	41.3	64	3	33	1.94
2-Cl	44.5	62	4	32	1.94
2-F	15.4	64	3	33	1.94
2,6-Br_2		no reaction			
2,6-Cl_2		no reaction			

[a] k_T/k_B values are measured with an accuracy of ±4 or better.

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pyridinium ions **4b**, **5b**, and **6b** with reduced steric inhibition to resonance, reacted readily at room temperature. The nitration selectivity in competitive experiments was measured (Table I). For comparison, we prepared and isolated *N*-nitro-2,6-dimethylpyridinium (lutidinium) salt **7**.[7] The K_T/K_B value was 35.1 ± 4 in good agreement with the literature value (39).[6]

2-Bromo- and 2-chloronitro onium ions show similar reactivity, despite the differing bulk of the halogens, and are both slightly less reactive than the lutidinium salt. 2-Fluoro-*N*-nitro onium cation **6b** is much more reactive (less selective) indicative of a weaker N–N bond (increased $-I$ effect of fluorine). In agreement with previous results,[6] despite differing reactivities, the regioselectivity remains almost constant.

Olah et al.[7] demonstrated that in N-nitration of 4-nitropyridine an irreversible isomerization from *N*-nitro to *N*-nitrito onium ion took place at elevated temperatures or by prolonged reaction time. The nitrito onium salts were shown not to be transfer-nitrating agents. To check possible nitrito onium ion formation, we prepared an authentic sample of the nitrito onium salt **8** by reacting the corresponding *N*-oxide[8] with $NO^+BF_4^-$. Comparison of the ^1H NMR of the two ions clearly showed them to be different. With **1b** the H_4 triplet is more downfield than the H_3 protons (doublet), whereas in the nitrito onium ion, the reverse was observed. In addition, hydrolysis of the nitrito salt gave the *N*-oxide, whereas **1a** gave only **1** and no *N*-oxide could be detected (GC). Thus, possible nitro → nitrito isomerization was excluded.

To probe the steric effects, the structure of the dihalo- and halo-*N*-nitro onium ions were compared with quinolinium and lutidinium cations by space-filling models and by energy minimization using MMX (PCMODEL); **1b** and **2b** were found to be very similar to lutidinium cation. Restricted N–N rotation was observed, with the plane of the nitro group perpendicular to the aromatic plane. Energy minimization showed that in the minimized structure of **1b** and **2b**, whereas the N–N bond itself remained in the aromatic plane (179°), the nitro group was orthogonal. With the monohalo-*N*-nitro and quinolinium cations, the N–N bond tilted slightly away from the substituent toward the unsubstituted 6-position.

Thus molecular modeling failed to indicate important structural (steric) differences which could be attributed to lack of reactivity.

Apart from a change in inductive effects, an important difference between the dihalo onium ions with the lutidinium cation is the presence of nonbonded electrons on halogens. Whereas p-π overlap is a major controlling factor for regioselectivity of ring nitration, mesomeric perturbation should not effectively alter the N–N bond reactivity.

We propose that the observed lack of reactivity of the dihalo-*N*-nitro onium ions may result from orbital overlap between the nitro p-orbital with a suitably aligned halogen lone pair and may be viewed as neighboring group participation by halogens, a well-known phenomenon in carbocation chemistry. Whereas similar participation could occur in the monohalo systems, nucleophilic attack by the aromatic could occur from the less hindered site, away from that orbital (position 6). A formal four-membered bromonium ion is probably not involved due to its high strain. It is interesting, however, to note that a four-membered cyclic bromonium ion was, in fact, observed under persistent ion condition at low temperature.[9] We are unaware of any halonium ion formation involving formal bonds to atoms other than carbon.[10]

Experimental Section

All reagents used were high purity commercial samples. Solvents were rigorously dried and stored over molecular sieves. Spectrograde CH_3CN (Aldrich) was used as received. $NO_2^+BF_4^-$ (Aldrich) was used without further purification. Its purity was determined as ca. 85% by nitration of nitrotoluene according to Ridd et al.[11] NMR spectra were recorded on a GN-300 wide-bore and a Varian FT-80 instruments. IR spectra were recorded on a Perkin-Elmer 1600 series FT-IR (mull in dry Nujol). GC analyses were performed with a Hewlett-Packard 5890 GC, equipped with an HP OV101 capillary column. Reported GC yields are after response factor correction.

C-Nitration of 1 and 2. A solution of **1** (1.49 g, 6.22 mol) in anhydrous CH_3CN (20 mL) was prepared in the glovebox. To the stirred solution was added slowly $NO_2^+BF_4^-$ (1.65 g, 12.44 mmol; 2 equiv). The solution was transferred to the hood and heated to reflux under dry N_2 for 20 h while being monitored via GC. The reaction mixture was quenched (saturated aqueous bicarbonate; 50 mL), extracted (CH_2Cl_2; 3 × 50 mL), dried ($MgSO_4$), and filtered. Removal of the solvent in vacuo yielded 1.63 g of a black crystalline compound, GC analysis of which slowed starting material (26.6%) and **1a** (73.3%). **1a** was isolated by column chromatography (hexane/CH_2Cl_2, 1:1) as white crystals: 0.85 g, 47.9%; mp 70–71 °C; ^1H NMR ($CDCl_3$) 8.20 (d, J = 8.1 Hz), 7.77 (d, J = 8.1 Hz).

Using the same procedure as above (starting with **2**), 1.24 g of a black crystalline solid was isolated, GC of which indicated **2** (22.8%) and **2a** (77.2%). The *C*-nitro product was isolated by column chromatography (hexane/CH_2Cl_2, 1:1) as white crystals (0.43 g, 39.8%): ^1H NMR (CD_3CN) 8.35 (d, J = 8.4 Hz), 7.61 (d, J = 8.4 Hz).

N-Nitration of 1 and 2. A solution of **1** (1.8 g, 7.5 mmol) in anhydrous CH_2Cl_2 (20 mL) was prepared with stirring in the glovebox. To the solution was slowly added $NO_2^+BF_4^-$ (0.5 g, 3.76 mmol; 0.5 equiv). The reaction mixture was transferred to the hood and heated to 50 °C under dry nitrogen for 24 h. The mixture was then returned to the glovebox, and the tan powder was filtered, washed repeatedly with anhydrous CH_2Cl_2 followed by one rinse with a benzene solution in CH_2Cl_2 (to remove any unreacted $NO_2^+BF_4^-$). GC of the benzene wash indicated trace amounts of nitrobenzene. The solid was repeatedly rinsed with CH_2Cl_2 and dried in vacuo to give **1b** (0.6 g, 42.8%): ^1H NMR (CD_3CN)[12] 8.23 (t, J = 7.7 Hz), 8.10 (d, J = 7.7 Hz).

Following the above procedure, to **2** (1.114 g, 7.53 mmol; 2 equiv) in dry CH_2Cl_2 was added $NO_2^+BF_4^-$ (0.5 g, 3.76 mmol; 0.5 equiv). Upon reflux, **2b** precipitated and isolated (0.52 g, 49%). GC of the benzene solution wash of the precipitate indicated no nitrobenzene was present: ^1H NMR (CD_3CN) 8.49 (t, J = 8.3 Hz), 7.94 (d, J = 8.3 Hz).

Attempted N-Nitration of 3. Following the above procedure, to **3** (0.867 g, 7.53 mmol) was added $NO_2^+BF_4^-$ (0.5 g, 3.76 mmol; 0.5 equiv). No *N*-nitropyridinium salt was formed after reflux in CH_2Cl_2. Workup of the organic phase and removal of the unreacted **3** gave **3a** (0.118 g; 19.6%): ^1H NMR (CD_2Cl_2) 8.70 (m), 7.06 (dd, J = 3.2 and 8.6 Hz).

In Situ Nitration of 3. A solution of **3** (0.06 g, 0.52 mmol) in CD_3CN (1 mL) was prepared with stirring in the glovebox. The solution was cooled to 0 °C, and $NO_2^+BF_4^-$ (0.069 g, 1 equiv) was added. The solution was allowed to reach room temperature, vigorously mixed for 20 min, and transferred into an NMR tube. ^1H NMR indicated only a mixture of **3** and **3a** (26%).

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(12) Spectra recorded in SO_2/CD_2Cl_2 and in $TfOH/SO_2/CD_2Cl_2$ at −65 °C were identical with that in CD_3CN at room temperature except for a slight change in the chemical shifts due to solvent and temperature.

Dehalogenation of 1a. A mixture of **1a** (0.75 g, 2.65 mmol) and benzoic acid (1.29 g; 4 equiv) was heated (180 °C). To the melt was added copper (1.009 g; 6 equiv) slowly over 3 min with stirring. The mixture was heated for an additional 5 min and allowed to reach room temperature, the solid was digested with saturated aqueous Na_2CO_3, and the mixture was partitioned with CH_2Cl_2. The organic phase was extracted and dried and the solvent was removed in vacuo. The crude product (0.145 g; yellow oil) was purified by column chromatography (alumina, ethyl acetate) to give 3-NP (0.074 g; 22.7%): mp 43-38.5 °C (lit 39 °C);[13] ^{1}H NMR (CD_2Cl_2) 9.36 (d, J = 2.2 Hz), 8.90 (d, J = 4.3 Hz), 8.50 (dd, J = 1.6 and 7.5 Hz), 7.60 (dd, J = 8.4 and 4.7 Hz).

N-Nitration of 4 and 5. To a solution of **4** (0.82 g, 5.24 mmol) in dry CH_2Cl_2 (20 mL) was added $NO_2^+BF_4^-$ (0.827, 6.23 mmol; 1.2 equiv) under nitrogen with efficient magnetic stirring. Upon reflux (24 h), the precipitated **4b** was isolated without washing with benzene (0.466 g; 31%). ^{1}H NMR [CD_3CN, 8.63 (dd, J = 1.5 and 6 Hz), 8.46 (dt, J = 1.5 and 8.0 Hz), 8.20 (d, J = 8 Hz), 8.01 (dt, J = 1.5 and 6 Hz).

To a solution of **5** (0.85 g, 7.53 mmol) in dry CH_2Cl_2 (20 ml) was added $NO_2^+BF_4^-$ (0.5 g, 3.76 mmol; 0.5 equiv). Upon reflux (24 h) the precipitated **5b** was isolated without a benzene wash (0.228 g; 24.6%): ^{1}H NMR (CD_3CN) 8.64 (dd, J = 1.5 and 5.8 Hz), 8.58 (dt, J = 1.7 and 8 Hz), 8.07 (d, J = 8.2 Hz), 8.01 (dt, J = 1.3 and 6.8 Hz).

Attempted C-Nitration of 4 and 5. In a typical experiment, to solution of the substrate (1.88 mmol) in anhydrous acetonitrile (20 mL) prepared in the glovebox was added $NO_2^+BF_4^-$ (2 equiv) with magnetic stirring at room temperature. The reaction mixture was transferred to the hood and heated to reflux under dry nitrogen for 24 h. GC analysis of the organic phase following workup showed no C-nitration.

N- and C-Nitration of 6. To a solution of **6** (0.73 g, 7.53 mmol) in dry CH_2Cl_2 was added $NO_2^+BF_4^-$ (0.5 g, 3.76 mmol; 0.5 equiv) under dry nitrogen with magnetic stirring. Upon reflux, **6b** precipitated. The salt was thoroughly shaken with a solution of benzene/toluene (1:1) diluted in methylene chloride and vacuum dried (0.406 g; 46.9%): ^{1}H NMR (CD_3CN) 8.73 (appearance q, J = 7.6 Hz), 8.51 (d, J = 3.9 Hz), 7.91 (distorted t, J = 6.8 Hz), 7.79 (m); ^{19}F NMR -81.7 (CF) and -150 ppm (BF_4^-).

GC analysis of the toluene/benzene solution showed trace amounts of nitrotoluene isomers and nitrobenzene with a K_T/K_B = 2.25, indicative of nitration by unreacted $NO_2^+BF_4^-$. GC analysis of the organic phase, following the removal of **6b** from the reaction mixture, showed two peaks for **6** (94%) and **6a** (6%) with the latter having a longer retention time. Unreacted **6** was removed by vacuum distillation, and **6a** was isolated (0.003 g, 6%): ^{1}H NMR ($CDCl_3$) 9.08 (s), 8.66 (m), 7.25 (m).

N-Nitration of 2,6-Dimethylpyridine (Lutidine). To a solution of lutidine (0.807 g, 7.53 mmol) in 20 mL of dry CH_2Cl_2, prepared with stirring at -20 °C in the glovebox was added $NO_2^+BF_4^-$ (0.5 g, 3.76 mmol; 0.5 equiv). After 20 min, the solution was diluted with 20 mL of dry CCl_4 and cooled to -20 °C for 24 h. The resulting tan crystals were filtered in the glovebox and dried in vacuo without washing with benzene, to give **7** (0.687 g, 75%): ^{1}H NMR 8.27 (t, J = 8 Hz), 7.61 (d, J = 7.8), 2.68 (s).

N-Nitrito-2,6-dibromopyridine (8). To a solution of *N*-oxide (1.1 g, 5.93 mmol) in 20 mL of dry CH_2Cl_2 was added $NO^+BF_4^-$ (0.25 g, 2.14 mmol; 1 equiv) inside the glovebox. The solution was transferred to the fume hood and heated to reflux under dry nitrogen for 24 h. The yellow precipitate was filtered and washed with CH_2Cl_2 and the product dried in vacuo (0.162 g, 19.1%): ^{1}H NMR (CD_3CN)[14] 8.26 (q, J = 8 Hz), 8.02 (t, J = 7.8 Hz).

Transfer-Nitration. In a typical experiment the pure *N*-nitropyridinium salts (1.5 mmol) was added with vigorous magnetic stirring to a solution of benzene and toluene (1:1; 5 equiv) diluted to 1 M with dry CH_3CN under dry nitrogen. The reaction progress was monitored by GC. In cases where no reaction was observed (**1b** and **2b**) the mixture was heated under reflux (24 h). The solvent and the aromatics were distilled off to give unchanged **1b** or **2b** (NMR). A portion of the recovered **1b** was quenched with saturated aqueous bicarbonate, extracted (CH_2Cl_2), and dried ($MgSO_4$). GC analysis showed only 1.

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Supplementary Material Available: ^{1}H NMR data for **1a**, **2a**, **1b**, **2b**, 3-NP, **3**, **3a**, **4b**, **5b**, **6**, **6a**, **6b**, **7**, **8**, ^{19}F NMR data for **6b** and **6**, and IR spectral data for **1a**, **2a**, **1b**, **2b**, 3-NP, **6**, **6b**, and **8** (27 pages). Ordering information is given on any current masthead page.

(13) Schickh, O. V.; Binz, A.; Schulz, A. *Ber.* **1936**, *69*, 2593.

(14) Unlike the nitro onium ion **1b**, the nitrito salt was totally insoluble in SO_2. In $TfOH/SO_2$ solvent (-60 °C) the spectrum consisted of a doublet at 8.26 and a broad triplet at 8.14 ppm.

Conformationally Restricted Arginine Analogues

Thomas R. Webb*,† and Charles Eigenbrot

Department of Medicinal and Biomolecular Chemistry, Genentech Inc., 460 Point San Bruno Blvd., South San Francisco, California 94080

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We report the practical synthesis and structural characterization of a set of conformationally constrained protected arginine analogues. These enantiomerically pure analogues have the general structure **1** and are prepared in seven to eight steps from the commercially available isomers of 4-hydroxyproline. These analogues vary in side chain length and in relative and absolute stereochemistry and are suitable for the direct introduction into peptides. The resulting peptide analogues should be useful as enzymatically stable replacements for bioactive peptides and as probes for understanding the conformational aspects of protein-peptide interactions.

Introduction

The synthesis of conformationally restricted amino acid analogues which can be incorporated into peptides is of interest in the investigation of protein-peptide interaction. Although there has been significant recent interest in the synthesis of conformationally constrained amino acid analogues,[1] there has been no report of the methodical design and preparation of a series of structurally kindred

†Present address: Corvas, Inc., 3030 Science Park Road, San Diego, CA 92121.

(1) For example, see: Rapoport, H.; Wolf, J.-P. *J. Org. Chem.* **1989**, *54*, 3164-3173. DiMaio, J.; Belleau, B. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1687-1689.

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