Reactions of Isocyanides and Pyridinium Triflates − A Simple and Efficient Route to Imidazopyridinium Derivatives

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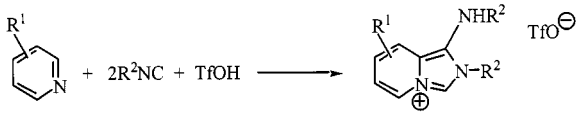
Keywords: Cycloadditions / Isocyanides / Nitrogen heterocycles

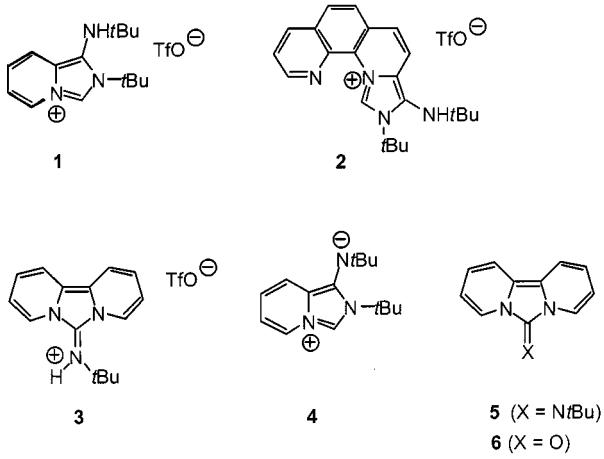
Imidazo[1,5-*a*]pyridinium derivatives are easily synthesized by reaction of pyridinium triflates in pure isocyanide. The compounds obtained by treatment of pyridinium, 1,10-phenanthrolinium and 2,2′-bipyridinium triflates with *tert*-butyl isocyanide are described, along with the crystal structures of the latter two.

Introduction

Isocyanides are versatile reagents in organic chemistry, especially for the synthesis of heterocyclic compounds.[1] Of major importance are multicomponent reactions with isocyanides which permit the building of large compound libraries in combinatorial chemistry.[2] In many of these multistep and one-pot condensations,[3−7] such as the Ugi transformation,[3] the key step is the reaction of the RNC molecule with an iminium ion or a protonated azabutadiene species. While these reactions of isocyanides are well documented, it seems that their reactivity towards pyridinium salts has been practically neglected. A noticeable exception is the reaction of pyridines with methyl chlorothioimidates and isocyanides, leading to 1-amino-3-(methylthio)imidazo[1,5-*a*]pyridinium chlorides, which would involve an *N*-imidoylpyridinium salt as the key intermediate.[7] We found that isocyanides react with pyridinium triflates, providing a practical route to imidazo[1,5-*a*]pyridinium derivatives, as shown in Scheme 1. Such compounds, which are rather uncommon,[7,8] exhibit interesting catalytic and pharmacological activities, but even though several procedures for their preparation have been described, these are far from simple. Here we report on two representative examples of this novel reaction with the synthesis of compounds **1** and **2** from pyridine and 1,10-phenanthroline, respectively; we also present the distinct reaction of $[bipyH_2][OTf]_2$ (bipy = 2,2′-bipyridine; OTf = OSO_2CF_3) with *t*BuNC which constitutes a simple access to the new urea derivative **3**.



Scheme 1. Synthesis of imidazo[1,5-*a*]pyridinium derivatives



Results and Discussion

Addition of triflic acid (TfOH) to pyridine in *tert*-butyl isocyanide led to the formation of compound **1**, resulting from the cyclocondensation of two *t*BuNC molecules with the pyridinium salt. After 24 h at 20 °C, the reaction solvents were evaporated to dryness and the product was washed with diethyl ether and isolated as colourless microcrystals in 61% yield. A similar result was obtained when *t*BuNC was replaced with *cyclo*-$C_6H_{11}NC$. A possible mechanism of this three-component transformation (Scheme 2) involves the pyridinium triflate as the first intermediate since $[C_5H_5NH][OTf]$ was found to react in pure *t*BuNC, giving **1** in 71% yield. The following step is the α-addition of $[C_5H_5NH]^+$ to *t*BuNC with formation of $[C_5H_5N{-}CH{=}NtBu]^+$;[9] this latter then undergoes a [4 + 1] cycloaddition with another *t*BuNC molecule and the final product is obtained by subsequent imine-enamine tautomerism. This mechanism is very similar to that proposed

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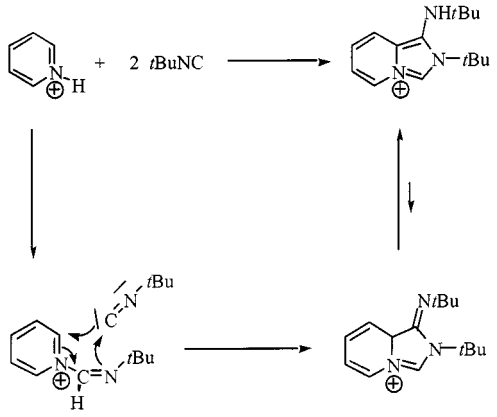
for the aforementioned reaction of azines with methyl chlorothioimidates and isocyanides.[7] The cycloaddition step is reminiscent of the cyclocondensation reactions of isocyanides with protonated diazabutadienes, which represent efficient routes to mono heterocyclic compounds.[5,6] Such a [4 + 1] cycloaddition was also proposed as the key step in the three-component condensation of amidines, aldehydes and isocyanides, leading to fused 3-aminoimidazoles.[4]



Scheme 2. Possible mechanism for the synthesis of imidazo[1,5-*a*]pyridinium derivatives

The reaction represented in Scheme 1 was extended to a number of substituted pyridinium triflates to give a series of aza-indoliziniums with the imidazo[1,5-*a*]pyridine nucleus.[10] For example, treatment of the phenanthrolinium salt [phenH][OTf][11] (phen = 1,10-phenanthroline) with *t*BuNC gave compound **2** which, after the usual workup, was obtained as yellow microcrystals in 52% yield. X-ray diffraction analysis revealed that the crystals of **2** exist in two polymorphic forms, one of which is shown in Figure 1. In both structures the cations exhibit very similar geometrical parameters. The phenanthroline moiety is characterized by some degree of localisation of the double bonds whereas the short C(2)−N(3) bond indicates that a positive charge is present on N(3), in addition to N(1) and N(2), and reflects a greater electronic delocalisation in the imidazonium ring system. The triflate anion is linked to the cation via the N(3)−H−O(1) bond; the N(3)−O(1) distance in each polymorph is equal to 2.969(4) and 3.129(3) Å, respectively. Similar features were observed in the crystal structures of **1** and its derivatives.[10]

The reaction with $[bipyH_2][OTf]_2$ [11] followed a different course since a single *t*BuNC molecule was condensed to the two nitrogen atoms of the bipy moiety; the yellow microcrystalline powder of **3** was isolated in 63% yield. The ring-closure reaction leading to **3** is clearly facilitated by the greater flexibility of bipy than phen. This flexibility is reflected in the crystal structure of **3** (Figure 2) with the angles C(4)−C(5)−C(6) and C(5)−C(6)−C(7) which are equal to 134.1 and 134.9° respectively. Partial delocalisation in the N(1)−N(2)−N(3)−C(11) fragment is indicated by the equal C−N bond lengths of 1.36 Å.

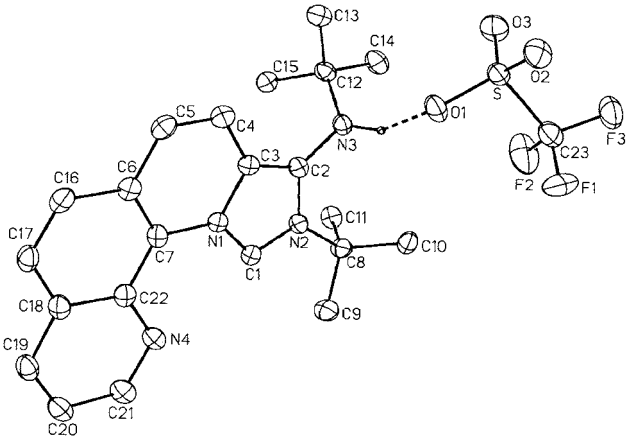


Figure 1. Structure of one of the two polymorphs of **2** in the crystal (thermal vibrational ellipsoids 30%); selected bond lengths [Å] and angles (°): C(1)−N(1) 1.337(4), C(1)−N(2) 1.329(4), C(2)−C(3) 1.362(4), C(2)−N(2) 1.409(4), C(3)−N(1) 1.408(4), C(2)−N(3) 1.391(4), C(8)−N(2) 1.511(4), N(1)−C(1)−N(2) 109.7(3), C(1)−N(2)−C(2) 108.9(3), C(1)−N(1)−C(3) 107.7(3), N(2)−C(2)−C(3) 106.1(3), C(2)−C(3)−N(1) 107.7(3)

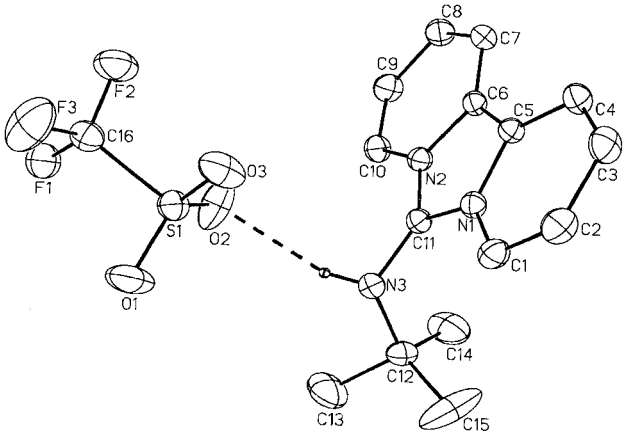


Figure 2. Structure of **3** in the crystal (thermal vibrational ellipsoids 30%); selected bond lengths [Å] and angles (°): N(1)−C(11) 1.356(4), N(2)−C(11) 1.366(4), N(1)−C(5) 1.394(4), N(2)−C(6) 1.400(4), C(5)−C(6) 1.385(4), N(2)−C(10) 1.394(4), C(6)−C(7) 1.411(4), C(7)−C(8) 1.346(4), C(8)−C(9) 1.423(4), C(9)−C(10) 1.352(4), N(3)−C(11) 1.369(4), N(1)−C(11)−N(2) 106.0(2), C(5)−N(1)−C(11) 110.7(2), C(6)−N(2)−C(11) 110.4(2), N(1)−C(5)−C(6) 106.7(2), N(2)−C(6)−C(5) 106.1(2), C(4)−C(5)−C(6) 134.1(3), C(5)−C(6)−C(7) 134.9(3)

Compound **1** was readily and quantitatively deprotonated with NaH in tetrahydrofuran (THF) at 20 °C to give the zwitterionic species **4**, which was transformed back into **1** upon addition of pyridinium triflate (NMR experiments). Treatment of **3** with NaH in THF gave the neutral compound **5** (X = N*t*Bu) which was converted upon alkaline hydrolysis into the imidazolone **6** (X = O). This latter and its chalcogen derivatives (X = S, Se, Te) have been recently isolated from trapping reactions of the parent dipyridoimidazo-2-ylidene, a formal 1:1 complex between singlet carbon and bipy.[12]

In conclusion, we have discovered a new reaction of isocyanides with pyridinium triflates which represents an efficient route to imidazo[1,5-*a*]pyridinium derivatives. This synthesis is more practical and general than those previously reported.

Experimental Section

All reactions were carried out under argon using standard Schlenk vessel and vacuum-line techniques.

Syntheses

1: Freshly distilled triflic acid (11 μL, 0.12 mmol) was added to a mixture of pyridine (10 μL, 0.13 mmol) and *t*BuNC (0.2 mL, 1.76 mmol). The reaction mixture slowly turned red and after 24 h at 20 °C, the excess isocyanide was evaporated off. The residue was washed with diethyl ether, eliminating a red oil, and the colourless powder of **1** was dried under vacuum (30 mg, 61%). ^{1}H NMR (200 MHz, [D$_8$]THF): δ = 9.77 (s, 1 H), 8.63 (d, *J* = 7.0 Hz, 1 H), 7.61 (d, *J* = 9.0 Hz, 1 H), 7.0 (dt, *J* = 9 and 7 Hz, 1 H), 6.88 (t, *J* = 7.0 Hz, 1 H), 4.10 (s, 1 H, NH), 1.80 and 1.25 (2 × s, 2 × 9 H). ^{13}C NMR (50.32 MHz, [D$_8$]THF): δ = 128.6, 127.9, 127.1, 125.3, 123.6, 118.3, 116.8, 63.2, 54.5, 30.8, 29.9. $C_{16}H_{24}F_3N_3O_3S$ (395.4): calcd. C 48.60, H 6.12, N 10.63; found C 48.53, H 6.12, N 10.73.

2: A mixture of [phen][OTf] (230 mg, 0.70 mmol) and *t*BuNC (4 mL, 35 mmol) was stirred for 18 h at 100 °C. The red suspension was evaporated to dryness and after several washings with diethyl ether, the yellow powder of **2** was dried under vacuum (180 mg, 52%). Crystals suitable for X-ray diffraction analysis were obtained from THF/diethyl ether. ^{1}H NMR (200 MHz, [D$_2$]dichloromethane): δ = 11.78 (s, 1 H), 9.20 (dd, *J* = 6 and 2 Hz, 1 H), 8.48 (dd, *J* = 8 and 2 Hz, 1 H), 8.10 (d, *J* = 8.0 Hz, 1 H), 7.94 (d, *J* = 8.0 Hz, 1 H), 7.92 (d, *J* = 10.0 Hz, 1 H), 7.75 (dd, *J* = 8 and 6 Hz, 1 H), 7.61 (d, *J* = 10.0 Hz, 1 H), 3.63 (s, 1 H, NH), 1.97 and 1.37 (2 × s, 2 × 9 H). $C_{23}H_{27}F_3N_4O_3S$ (496.5): calcd. C 55.63, H 5.48, N 11.28; found C 55.51, H 5.55, N 11.41.

3: By using a similar procedure as for **2**, a yellow powder of **3** was obtained in 63% yield by reacting [bipyH$_2$][OTf]$_2$ (354 mg, 0.77 mmol) and *t*BuNC (5 mL, 44 mmol) for 6 days at 20 °C. ^{1}H NMR (200 MHz, [D$_8$]THF): δ = 8.80 (d, *J* = 7.0 Hz, 2 H), 8.33 (d, *J* = 9.0 Hz, 2 H), 7.35 (t, *J* = 7.0 Hz, 2 H), 7.23 (dd, *J* = 9 and 7 Hz, 2 H), 6.11 (s, 1 H, NH), 1.27 (s, 9 H). $C_{16}H_{18}F_3N_3O_3S$ (388.4): calcd. C 49.35, H 4.66, N 10.79; found C 49.20, H 4.66, N 10.95.

4: In an NMR tube, NaH (5 mg, 0.21 mmol) was added to a suspension of **1** (9 mg, 0.02 mmol) in [D$_8$]THF (0.3 mL). Evolution of gas was immediately observed and the spectrum of the purple solution showed the quantitative formation of **4**. ^{1}H NMR (200 MHz, [D$_8$]THF): δ = 7.65 (s, 1 H), 7.04 (d, *J* = 9.0 Hz, 1 H), 6.94 (d, *J* = 7.0 Hz, 1 H), 5.95 (t, *J* = 7.0 Hz, 1 H), 5.19 (dd, *J* = 9 and 7 Hz, 1 H), 1.58 and 1.18 (2 × s, 2 × 9 H). Compound **4** was transformed back into **1** upon addition of pyridinium triflate (5 mg, 0.023 mmol).

5: Compound **3** (203 mg, 0.52 mmol) was treated with NaH (50 mg, 2.1 mmol) in THF (20 mL). Evolution of gas was immediately observed and the colour of the solution changed from yellow to red. The solution was evaporated to dryness and **5** was extracted in pentane and isolated as a red powder after evaporation and drying under vacuum (119 mg, 95%). ^{1}H NMR (200 MHz, [D$_8$]THF): δ = 7.71 (d, *J* = 6.0 Hz, 2 H), 7.11 (d, *J* = 9.5 Hz, 2 H), 6.14 (dd, *J* = 9.5 and 8 Hz, 2 H), 6.05 (dd, *J* = 8 and 6 Hz, 2 H), 1.35 (s, 9 H). $C_{15}H_{17}N_3$ (238.3): calcd. C 75.28, H 7.16, N 17.56; found C 75.09, H 7.27, N 17.74.

X-ray Crystallography

2: (one polymorph represented in Figure 1): $C_{23}H_{27}F_3N_4O_3S$, *M* = 496.55, crystal dimensions: 0.40 × 0.30 × 0.15 mm^3, monoclinic, space group $P2_1/n$, *a* = 16.844(3), *b* = 9.0290(18), *c* = 17.660(4) Å, β = 117.44(3)°, *V* = 2383.6(8) Å^3, *Z* = 4, ρ = 1.384 gcm^{-3}, μ(Mo-K_α) = 0.192 mm^{-1}, measured reflections 14657, 3904 independent, 2507 > 2σ(*I*), 307 parameters, *R*1 = 0.0546, *wR*2 = 0.1197, GOF = 0.995, residual electron density: max./min. 0.379/−0.417 eÅ^{-3}. The second polymorph of **2** was obtained in the same crystallisation batch and was crystallographically characterized: $C_{23}H_{27}F_3N_4O_3S$, *M* = 496.55, crystal dimensions: 0.30 × 0.20 × 0.20 mm^3, triclinic, space group $P\bar{1}$, *a* = 9.6870(19), *b* = 10.997(2), *c* = 12.201(2) Å, α = 65.47(3), β = 77.42(3)°, γ = 85.27(3)°, *V* = 1154.0(4) Å^3, *Z* = 2, ρ = 1.429 gcm^{-3}, μ(Mo-K_α) = 0.198 mm^{-1}, measured reflections 7044, 3564 independent, 2831 > 2σ(*I*), 325 parameters, *R*1 = 0.0489, *wR*2 = 0.1172, GOF = 0.752, residual electron density: max./min. 0.270/−0.375 eÅ^{-3}.

3: $C_{16}H_{18}F_3N_3O_3S$, *M* = 389.39, crystal dimensions: 0.30 × 0.25 × 0.20 mm^3, monoclinic, space group $P2_1/n$, *a* = 11.460(2), *b* = 8.5750(17), *c* = 18.150(4) Å, β = 95.34(3)°, *V* = 1775.9(6) Å^3, *Z* = 4, ρ = 1.456 gcm^{-3}, μ(Mo-K_α) = 0.234 mm^{-1}, measured reflections 11108, 2914 independent, 2081 > 2σ(*I*), 239 parameters, *R*1 = 0.0509, *wR*2 = 0.1118, GOF = 1.011, residual electron density: max./min. 0.406/−0.311 eÅ^{-3}. The data were collected on a Nonius Kappa CCD diffractometer with Mo-K_α radiation, at *T* = 123(2) K (**2**) or 223(2) K (**3**) and a scan range of 4.0 < 2θ < 50.0°. The structures were solved by direct methods and refined against F^2 for all observed reflections, with anisotropic thermal parameters for all non-hydrogen atoms. H atoms were introduced at calculated positions and constrained to ride on their parent carbon atom. Software used: SHELXTL-97, SHELXS-86, SHELXL-93 (G. M. Sheldrick, Universität Göttingen).

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-163740 and CCDC-163741 (**2**) and CCDC-163742 (**3**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) +44-1223/336-033; e-mail: deposit@ccdc.cam.ac.uk).

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[9] As suggested by the referees, this intermediate can also result from the reaction of pyridine with the imino-carbocation $[RN{=}CH]^+$.
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Received July 5, 2001
[O01334]