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Advantages of the Ns group in the reactions of N^1-SO_2R inosines with benzylamine and with $^{15}NH_3$

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Abstract—The reactivity of N^1-alkylsulfonyl- and N^1-arylsulfonyl-2′,3′,5′-tri-*O*-acetylinosine with benzylamine and with $^{15}NH_3$, regarding the attack on C2, has been shown to be in the order CF_3SO_2 (Tf) > 2,4-$(NO_2)_2C_6H_3SO_2$ (DNs) ⩾ 4-$NO_2C_6H_4SO_2$ (*p*Ns) ≈ $C_6F_5SO_2$ (PFBs) > 2-$NO_2C_6H_4SO_2$ (Ns) ≫ CH_3SO_2 (Ms) > 4-$CH_3C_6H_4SO_2$ (Ts) > 2,4,6-$(CH_3)_3C_6H_2SO_2$ (Mts). In spite of its intermediate reactivity, the Ns group is the most appropriate, since in this case the formation of by-products is minimised during the ring-opening and ring-closing steps of the process. Another advantage of the Ns group is thus disclosed.
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In 1991, it was discovered that N^3-nitro pyrimidine nucleosides underwent ring-opening–ring-closing (RORC) processes when treated with nitrogen nucleophiles.[1a,b] Shortly afterwards, the protocol was applied to N^1-nitro inosines (e.g., **1**).[1c,d] In these reactions, the NNO_2 group is replaced by ^{15}NH, NR, NNH_2, etc., which may be viewed as an exchange reaction of a very weak nucleophile (a leaving group, NH_2NO_2) for a stronger N-nucleophile ($^{15}NH_3$, NH_2R, NH_2NH_2, etc.). We took advantage of this novel reaction to synthesise a series of specifically ^{15}N-labelled nucleosides.[1e,f,g] Labelled nucleosides have many applications in RNA/DNA chemistry.[2]

Electron-withdrawing groups (EWGs) other than NO_2 could work similarly. In fact, Piccialli and co-workers reported the conversion of N^1-4-nitrophenyl- and N^1-2,4-dinitrophenyl-2′-deoxyinosines to [1-^{15}N]-2′-deoxyinosine;[3] owing to the relatively moderate EW character of these substituents, excesses of $^{15}NH_3$ and severe reaction conditions were required. In this context, it occurred to us that N^1-alkylsulfonyl- or N^1-arylsulfonylinosines (**2**)[4,5] could be more appropriate competitors of **1**. Indeed, the CF_3SO_2 group (Tf) is known to be a stronger EWG than the NO_2 group, according to their Hammett substituent constants and Swain–Lupton parameters (e.g., for Tf, $F = 0.74$ and $R = 0.22$, while for NO_2 $F = 0.65$ and $R = 0.13$).[6] The values corresponding to the benzenesulfonyl group (Bs) are also known (e.g., $F = 0.58$ and $R = 0.10$),[6a] so that it can be expected that nitrobenzenesulfonyl groups will show an EW character somewhat stronger than Bs, while the tosyl (Ts) and mesitylenesulfonyl (Mts) groups are expected to behave as slightly weaker EWGs. Anyway, the high number of available sulfonyl-containing substituents may permit the tuning of the EW power required. We have tested a set of these inosines (**2**, Scheme 1) against two representative amines, benzylamine and $^{15}NH_3$. The results throw light not only on the most suitable substituent for performing the desired N-alkylations and ^{15}N labellings, but also, from a more academic and general point of view, on the relative performance of SO_2R groups as EWGs.

Compounds **2** were prepared from natural inosine (1.0 mmol), by standard acetylation, followed by treatment with diisopropylethylamine (DIPEA, 1.2 mmol) and sulfonyl chlorides (1.2 mmol of CH_3SO_2Cl = MsCl, CF_3SO_2Cl = TfCl, etc.), in CH_2Cl_2 at room temperature for 1–8 h. The desired N^1-sulfonyl derivatives (**2a**–**h**) were obtained in 90–95% overall yields. Some reactions were repeated in the presence of catalytic amounts of 4-(dimethylamino)pyridine (DMAP) or with DMAP as a base and catalyst, with the same result: the N^1-substituted product was formed almost quantitatively.

The reactions of **2a**–**h** with $PhCH_2NH_2$ (2.0 equiv) in CH_3CN, mixing substrate and reagent at −30 °C and

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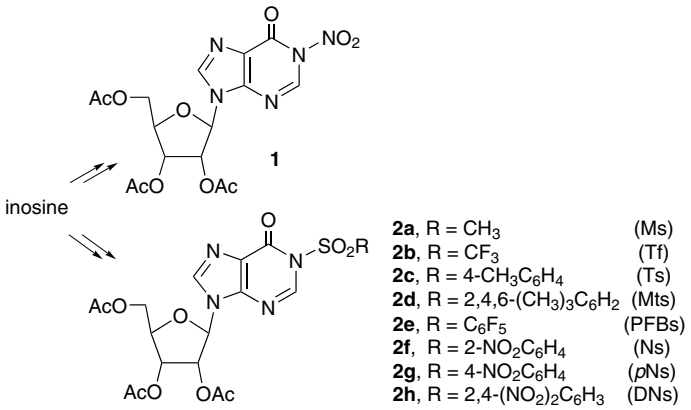
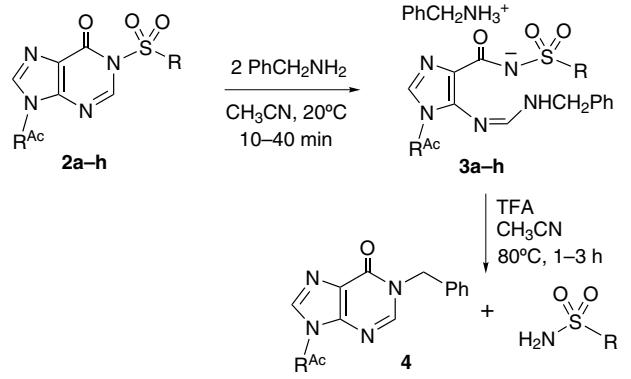


Scheme 1.



Scheme 2. Reaction of **2a**–**h** with benzylamine. By heating **3a**–**h**, in the presence of TFA, yields of **4** were 0% (from **2a**), 0% (**2b**), 47% (**2c**), 5% (**2d**), 10% (**2e**), 83% (**2f**), 52% (**2g**) and 62% (**2h**).

then stirring at 20 °C for 10–40 min (until all the starting material had disappeared), were first investigated. The desired open intermediates (**3a**–**h**, see Scheme 2, where only one of the four possible species in equilibrium is depicted), as well as other products (see below), were quickly formed. Although intermediates **3a**–**h** were stable at room temperature, by addition of CF_3COOH (TFA, 1 equiv) and heating for 1–3 h at 80 °C, several of them could be cyclised to N^1-benzylinosine **4**. It is remarkable that **2f** (the *o*-nosyl derivative, henceforward Ns) afforded the highest overall yield of **4** (83%). Despite the presence of two nitro groups in the phenyl ring, compound **2h** (the DNs derivative) only gave a 62% yield of **4**. Compounds **2g** (the *p*Ns derivative) and **2c** (the Ts derivative) afforded only moderate yields of **4**. Triflyl derivative **2b** did not cyclise at all![7]

Analyses of the final mixtures allowed us to determine that, besides **4** and sulfonamides NH_2SO_2R (the co-products of the desired reactions), they contained variable amounts of *N*-benzyl sulfonamides ($PhCH_2NHSO_2R$) and starting triacetylinosine (both coming from the attack of benzyl amine on the sulfur atom) and diverse decomposition by-products. In the case of **2h**, *N*-(2,4-dinitrophenyl)benzyl amine was also formed, arising from the attack on the S-linked carbon atom (S_NAr reaction followed by loss of SO_2). Attack of the nucleophile at C6, deacylation, or cleavage of the anomeric bond were not observed under our reaction conditions. The percentages of benzylamine attack on the "main" electrophilic sites, at room temperature, are summarised in Scheme 3. As expected, the percentages of desulfonylation were low or nil when there are Me or NO_2 substituents *ortho* to the sulfonyl groups.

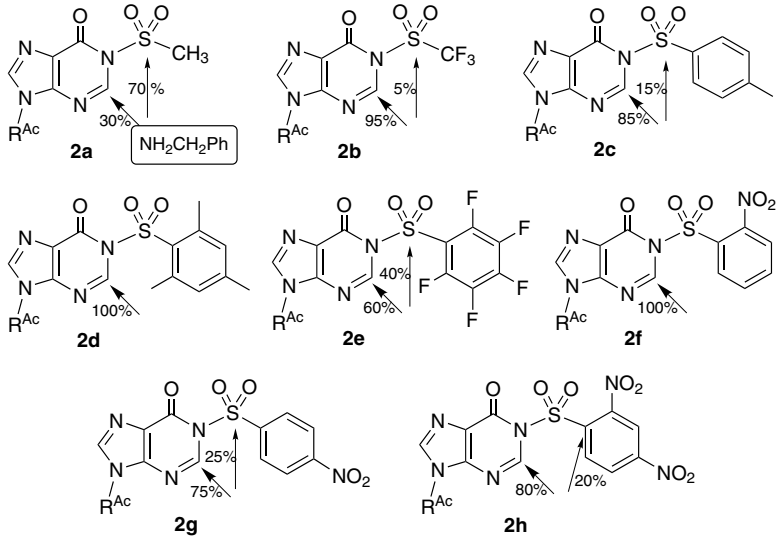
To confirm all these results, competition experiments were monitored by ^1H NMR spectroscopy. For instance, 0.2 mmol of each **2a** and **2b** were treated with 0.2 mmol of benzylamine in $CDCl_3$ at 0 °C, viz. under conditions in which we had noted that the attack on C2 was largely predominant; while **2a** remained intact, a high percentage of **2b** had undergone the ring opening within 1 h. Similar experiments were undertaken with other pairs. N-Nitro derivative **1** (which affords a 80% yield of **4** under identical conditions) was also included in the study, to evaluate its relative ring-opening rate. The reactivity order was

$$\mathbf{2b} > \mathbf{1} > \mathbf{2h} \geqslant \mathbf{2g} \approx \mathbf{2e} > \mathbf{2f} \gg \mathbf{2a} > \mathbf{2c} > \mathbf{2d}.$$

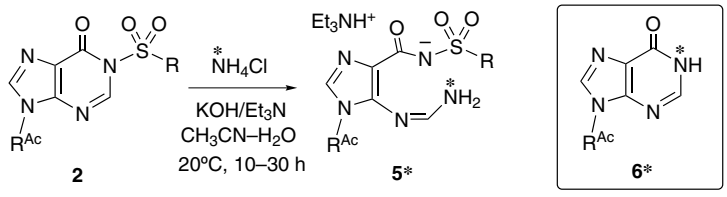
These results seem to correlate with the relative EW character, known or assumed, of the different groups, as discussed in the introduction. The trend may be useful for more general applications, such as in E2 reactions involving OSO_2R derivatives or in conjugate additions to unsaturated sulfones.

Reactions of $^{15}NH_3/Et_3N$ (1.10 equiv of $^{15}NH_4Cl$, 1.05 equiv of KOH and 1.10 equiv of Et_3N, in CH_3CN–H_2O at room temperature)[1] with **2** were then investigated (Scheme 4), searching for the most suitable groups for ^{15}N labelling. Open intermediates **5*** were formed in all cases, together with variable amounts of unlabelled triacetylinosine and sulfonamides $H_2N^*SO_2R$, both arising from the attack of $^{15}NH_3$ at the sulfur atom. Desulfonylation by-products were really inconvenient since, after the cyclisation step (conversion of **5*** to **6***), the desired [1-^{15}N]-2′,3′,5′-tri-*O*-acetylinosine (**6***) would be contaminated with large amounts of unlabelled material.

Therefore, we analysed more carefully the ratios of attack of $^{15}NH_3$ at the "main" electrophilic sites, in CH_3CN–



Scheme 3. Ratios of attack of benzylamine at different positions.



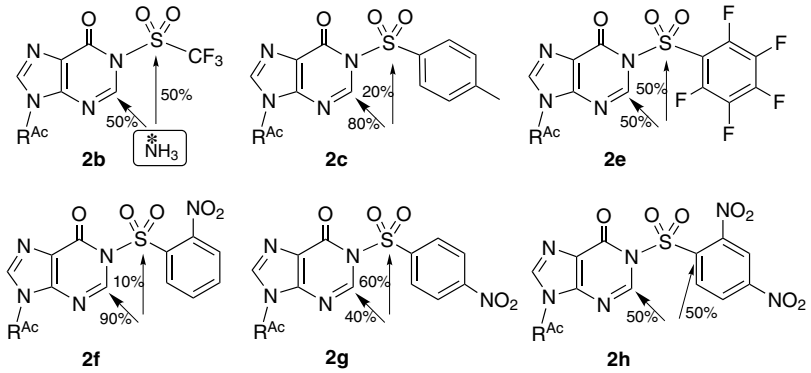
Scheme 4. Reaction of **2** with $^{15}NH_3$.

H_2O at room temperature. Since in preliminary experiments (preceding paragraph) we noted that desulfonylation largely predominates in the case of **2a** and that **2d** reacted too slowly, we only re-studied the other six compounds. The results are summarised in Scheme 5. We found that (i) compounds **2f** and **2c** underwent the smallest percentages of desulfonylation, (ii) Tf, PFBs and *p*Ns derivatives (i.e., **2b**, **2e** and **2g**) gave around 50% of desulfonylation, and (iii) **2h** underwent an indirect desulfonylation (attack on C_{ipso}, S_NAr reaction). Reactions with $^{15}NH_3$ were less chemoselective than with benzylamine.

In short, only **2f** and **2c** seemed suitable enough as starting materials for the preparation of **6***, since the other derivatives would afford a 50% labelled product at most.

Thus, to obtain **6***, we proceeded as follows: (i) after treatment of **2f** and **2c** with $^{15}NH_3$ as indicated above, **5f*** and **5c*** were isolated from by-products by column chromatography (with removal of Et_3N, affording the corresponding zwitterionic species **5f′*** and **5c′***, not shown in Scheme 4); (ii) these intermediates were then heated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 1.0 equiv) in anhydrous CH_3CN for 7 h. Yields of **6*** ($\geqslant$98% of ^{15}N) were 75% (from **2f**) and 20% (from **2c**). Again, the Ns derivative (**2f**) appeared to be the group of choice (affording yields of **6*** similar to those obtained from **1**).[1d]

In summary, in the reactions of N^1-EWG-substituted inosines with N-nucleophiles the order of reactivity,



Scheme 5. Ratios of attack of $^{15}NH_3$ at different positions.

regarding the ring-opening step (attack on C2), is that already indicated. In general, this ring-opening step is quite rapid, although the open intermediates are often contaminated by relatively significant percentages of desulfonylation by-products (by attack on the sulfur atom, or in the case of **2h** by attack on C_{ipso}). Difficulties also appear in the ring-closing step, since most intermediates of type **3** and **5*** decompose on heating more rapidly than they cyclise. The Tf group (see **2b**), of which we had reasonable expectations owing to its very strong EW character, is useless, for both the N-alkylation reaction and ^{15}N labelling. Surprisingly, the Ns group (see **2f**) affords the best yields of **4** and **6***, since it is the case in which the number and amount of by-products produced in both steps are minimal. Thus, another advantage of Ns as the activating or protecting group is now disclosed.

Acknowledgements

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Supplementary data

Selection of ^{1}H (400 MHz) and ^{13}C (100.6 MHz) NMR spectra, corresponding to compounds **2b**, **2c**, **2f**, **2g** and **2h**, intermediate **3f**, compound **4**, intermediate **5f′*** and compound **6***. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.05.137.

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7. On the other hand, on heating, without additives, only **3b** cyclised to **4**, even though in poor yield (30%).