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# *N*-Hydroxy indoles as flexible substrates in rearrangements—a novel reaction with activated triple bonds

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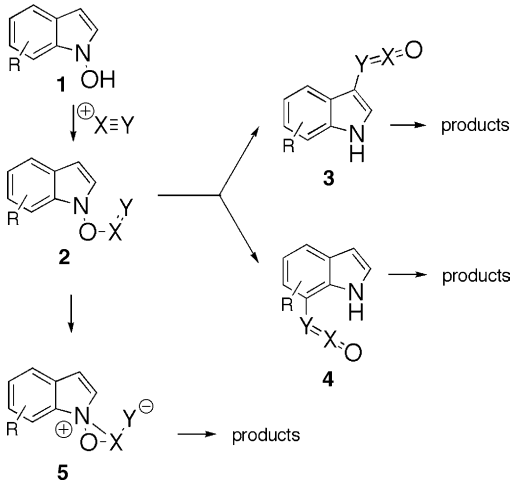
**Abstract**—A novel rearrangement of *N*-hydroxy indole derivatives obtained from addition of *N*-hydroxy indoles to the activated triple bonds of alkynes was found to coexist with 3,3-sigmatropic rearrangements to the indolic ring. A mechanism involving an intermediate oxaziridinium ring rationalizes the transformation.


*N*-Hydroxy indole derivatives of type **2**, obtained from **1** by reaction with unsaturated electrophiles $X{\equiv}Y^{+}$ are species capable in principle of suffering rearrangements to more than one position of the carbon framework of the indolic system, leading to either **3** or **4** (Scheme 1). Alternatively they can be envisaged to react via the three-membered ring species **5**, and lead to products derived thereof, but to our knowledge no record exists reporting this last possibility. We report here our results in the 3,3-sigmatropic rearrangements of derivatives **2** as well as a new rearrangement leading to products derived from the oxaziridinium species **5**.




**Scheme 1.** Rearrangements of *N*-hydroxy indole derivatives **2**.

Products resulting from 3,3-sigmatropic rearrangements of derivatives of enehydroxylamines (possessing the critical C=C—N—O system)[1,2] and aromatic hydroxylamines[3] have long been reported. There have been few instances where *N*-hydroxy indole derivatives have yielded compounds arising from such rearrangements.[4] For example, Somei isolated 3-acetoxy indole derivatives, from the transposition of *N*-acetoxy indoles. A similar reaction with 1-fluoro-2,4-dinitrobenzene attached the aromatic ring to the C-3 of the indolic framework.[5]

Typically when **1a**[6] was reacted in the presence of base such as DABCO (3 equiv) and cyanogen bromide (3 equiv) the unprecedented rearrangement to position 7 was observed, alongside the rearrangement to position 3.[7] In fact such is the explanation for the two types of compounds isolated, after work-up, that is, the 7-amino indole **6** (12%) and the dimeric **7** (19%). While **6**, isolated after acetylation to afford **6′** (82%), is the only product isolated from the rearranged **2′a**, the more exposed isocyanate group of **2″a** may be subject to further attack by the nucleophilic oxygen of **1a** leading to the heterodimer **7** (Scheme 2). The type of base used appeared to be critical. Thus when DABCO was substituted by $Et_3N$ the yield of **7** rose to 58%. When NaH was used the reaction

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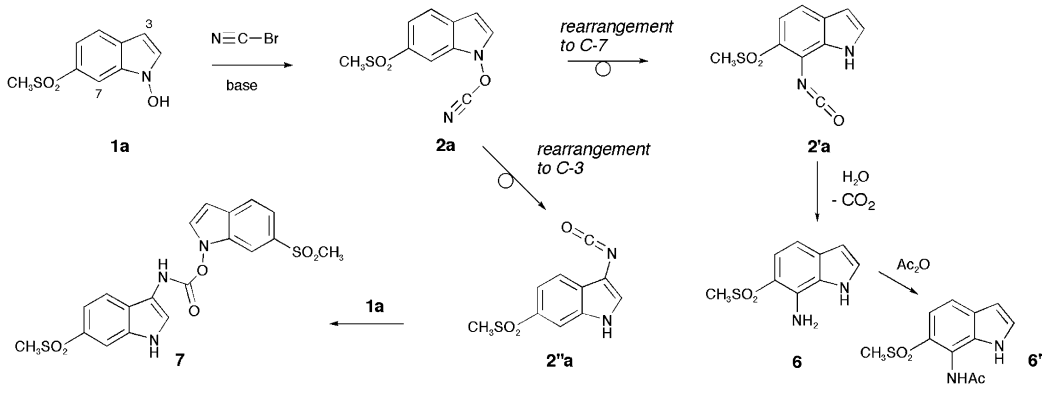


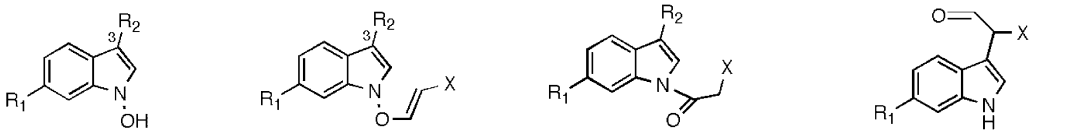

**Scheme 2.** Products of reaction of *N*-hydroxy indole **1a** with bromocyanogen.

mixture proved too complex for study. A different situation emerged when activated alkynes were used instead, and the results can be found in Table 1. For example, addition of **1a** to the acetylenic sulfone **8** gave the first isolable Michael product **9a** (Scheme 3), which displayed the characteristic coupling constant of $J_{1,2}$ of 12 Hz for the *trans* olefinic protons from sulfone moiety at $\delta$ 7.91 and 5.88. It rearranged exclusively to the indole 3 position to give **10a**, which lacked the proton at C-3, and had all the resonances of the aromatic protons of the sulfone and the starting indole. In $CDCl_3$ its $^1H$ NMR showed two sets of resonances, which were attributed to a keto-enol equilibrium (2:1), in particular one set of two doublets ($J$ 2.4 Hz) at $\delta$ 9.99 and 5.47 for, respectively, the aldehydic and α-proton of the keto form, and another set at $\delta$ 7.89 (doublet, $J$ 0.8 Hz) for the enolic form. Both forms showed resonances at ca. $\delta$ 9.7, exchangeable with $D_2O$, which were attributed to the free N–H.

However, more interestingly was the isolation from the same reaction of an isomeric **11a**. Its structure became apparent upon inspection of its $^1H$ NMR spectrum, which displayed the low-field resonance of H-7 at $\delta$ 8.84, *both* protons at H-3 and H-2, and a diagnostic 2H singlet at $\delta$ 4.69. A carbonyl at 1697 $cm^{-1}$ in the IR spectrum confirmed the amidic structure.

Its formation can be rationalized by invoking an attack of the indolic nitrogen on the adjacent activated double bond to give the oxaziridinium[8] related species **11′a**. Displacement of the negative charge to the adjacent carbon would lead to the ylide **11″a**, en route to the amide **11a**. The isomerization of oxaziridine into the corresponding amide has long been known,[9] the driving force being the release of steric strain from the three-membered ring, and the formation of the more stable amide functional group. Furthermore, the instability of the N-aromatic oxaziridine[10] would in our case ease this conversion.

**Table 1.** Products from reactions of *N*-hydroxy indoles and electrophiles containing activated triple bonds



**1a, b, c** **9a, b, c** (X=$SO_2C_6H_4CH_3$) **15a, b, c** (X=$CO_2Me$) **11a, b, c** (X=$SO_2C_6H_4CH_3$) **16a, b, c** (X=$CO_2Me$) **10a, b** (X=$SO_2C_6H_4CH_3$) **17a, b** (X=$CO_2Me$)

**a** $R_1$ = $SO_2CH_3$; $R_2$ = H **b** $R_1$ = H; $R_2$ = H **c** $R_1$ = H; $R_2$ = $CH_3$

| Entry | Starting *N*-hydroxy indole | Electrophile | Addition product[a] (yield/%) | Amide (yield[b]/%) | Rearrangement product to indole *C*-3 (yield[b]/%) |
|---|---|---|---|---|---|
| 1 | **1a** | *p*-$CH_3C_6H_4SO_2CCH$ (**8**) | **9a** (25)[b] | **11a** (19) | **10a** (10) |
| 2 | **1b** | *p*-$CH_3C_6H_4SO_2CCH$ (**8**) | **9b**[c] | **11b** (34) | **10b** (N.D.)[e] |
| 3 | **1c** | *p*-$CH_3C_6H_4SO_2CCH$ (**8**) | **9c**[c] | **11c** (35) | **10c** (N.D.)[e] |
| 4 | **1a** | Methyl propiolate | **15a** (24)[b] | **16a** (34) | **17a** (9) |
| 5 | **1b** | Methyl propiolate | **15b** (42)[d] | **16b** (25)[d] | **17b** (30)[d] |
| 6 | **1c** | Methyl propiolate | **15c**[c] | **16c** (14) | **17c** (N.D.)[e,f] |

[a] Reaction conditions: Addition of electrophile (1.1 equiv) to hydroxyindole **1** (1 equiv) and NaH (1.1 equiv) in dry THF at 0 °C, then rt. Work-up by acidification, extraction and PTLC ($SiO_2$, *n*-hexane–EtOAc, 75:25). The *Z*-olefin, though detected in the early stages of the reaction, rapidly isomerized to the *E*-isomer.

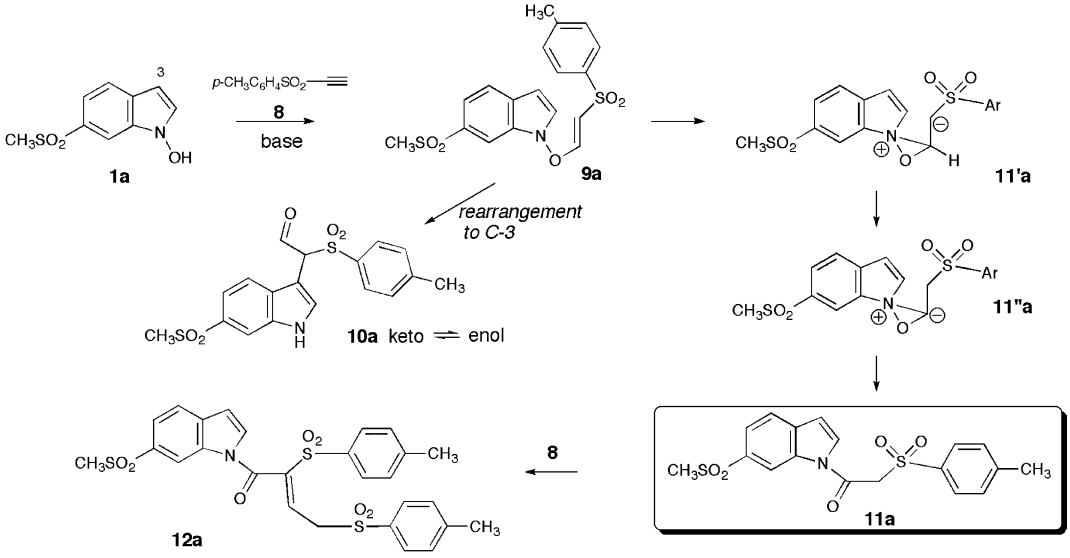
[b] Isolated.

[c] Compound detected by TLC ($SiO_2$, *n*-hexane–EtOAc, 66:34) not isolated.

[d] Yield by $^1H$ NMR, before separation of products.

[e] N.D. = not detected.

[f] Product **18** isolated (yield 4%) from a complex mixture.

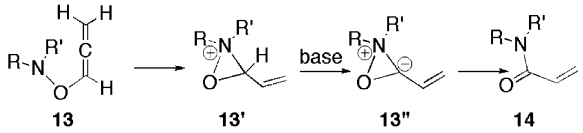



**Scheme 3.** Products of reaction of *N*-hydroxy indole **1a** with sulfone **8**.

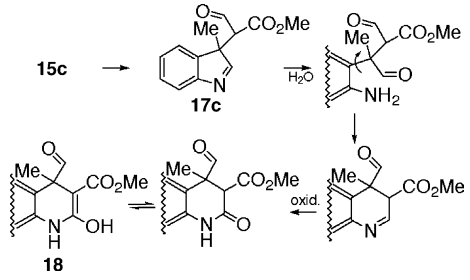
Compounds of type **11** can be useful in synthesis given the activation experienced by the methylene group. For example, in the presence of excess electrophile (2–3 equiv) **8**, **12a** was readily isolated (yield 39%) (Scheme 3).

A similar transformation was recently reported to occur in the rearrangement of propargyl *N*-oxides[11] to *O*-allenyl hydroxylamines **13**. These can give, on treatment with base,[12] acrylamide derivatives **14** through analogous oxaziridinium intermediates **13′** and **13″** (Scheme 4).

When using the methyl propiolate as the electrophile and **1a**, the analogue amidic product **16a** is produced from **15a** (see Table 1). Of interest is the fact that the 3-methyl *N*-hydroxy indole **1c** when reacted with methyl propiolate gave **18**, albeit in a low yield after aq work-up, the formation of which is shown below (Scheme 5). The possibility that the oxidation step results from the oxaziridinium species cannot be dismissed.[13]




**Scheme 4.** Rearrangements of *O*-allenyl hydroxylamines to amides.




**Scheme 5.** Formation of **18** from **15c**.

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6. Compound **1a** is comercially available from Peakdale Fine Chemicals, UK. Compounds **1b** and **1c** were synthesized by literature methods: (a) Henmi, T.; Sakamoto, T.; Kikugawa, Y. *Heterocyles* **1997**, *44*, 157–163; (b) Somei, M.; Kawasaki, T. *Heterocycles* **1989**, *29*, 1251–1254.
7. A common feature of all reactions of *N*-hydroxy indoles herein reported is the isolation of the corresponding indoles. All new compounds gave correct microanalyses and/or HRMS (EI). Selected data, $^1$H NMR (400 MHz, $CDCl_3$ unless stated otherwise): Compound **6**: $\delta$ 8.46 (br s, NH), 7.73 (d, $J = 8.8$ Hz, H-4), 7.31 (t, $J = 2.6$ Hz, H-2), 7.12 (d, $J = 8.8$ Hz, H-5), 6.53 (t, $J = 2.6$ Hz, H-3), 5.41 (br s, $NH_2$); Compound **7**: 10.31 (s, NH), 9.41 (s, NH′), 7.98 (br s, H-7), 7.93 (br s, H-7′), 6.53 (d, $J = 3.2$ Hz, H-3), 3.02 (s, $CH_3SO_2$), 3.01 (s, $CH_3'SO_2$); Compound **9a**: 7.91 (d, $J = 12$ Hz, HC=C*H*–O), 7.88 (br s, H-7), 7.42 (d, $J = 3.6$ Hz, H-2), 6.57 (d, $J = 3.6$ Hz, H-3), 5.88 (d, $J = 12$ Hz, *H*C=CH–O); Compound **10a** (keto-enol): 9.99 (d, $J = 2.4$ Hz, C(O)H), 9.71 (br s, NH), 9.67 (br s, NH′), 7.98 (s, H-7), 7.96 (s, H-7′), 7.89 (d, $J = 0.8$ Hz,

HOCC*H*′), 5.47 (d, $J = 2.4$ Hz, C*H*C(O)H); Compound **11a** ($CDCl_3$–acetone-$d_6$, 90:10): 8.84 (s, H-7), 6.70 (d, $J = 3.2$ Hz, H-3), 4.69 (s, $CH_2SO_2$); Compound **12a**: 8.83 (s, H-7), 7.21 (t, $J = 8$ Hz, C=C*H*$CH_2$), 6.66 (d, $J = 3.7$ Hz, H-3), 3.86 (d, $J = 8$ Hz, $CH_2SO_2$); Compound **16a**: 9.04 (s, H-7), 6.76 (d, $J = 4$ Hz, H-3), 4.02 (s, C*H*$_2CO_2Me$), 3.80 (s, $OCH_3$); Compound **17a**: 12.04 (d, $J = 12$ Hz, CHO*H*), 9.24 (br s, NH), 8.08 (br s, H-7), 7.38–7.34 (m, C*H*OH); Compound **18**: 13.0 (br s, OH), 9.96 (s, C(O)H), 7.50 (d, $J = 7.2$ Hz, H-5), 7.31 (t, $J = 7.4$ Hz, H-7), 7.20 (t, $J = 7.2$ Hz, H-6), 7.04 (d, $J = 7.4$ Hz, H-8), 6.81 (s, NH), 1.75 (s, 4-$CH_3$).

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