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The reaction of nitrones with pyrroles and furan: an easy access to heteroaromatic hydroxylamines and bis(heteroaryl)alkanes

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Abstract—*N*-Benzylnitrones react with heteroaromatic compounds such as pyrroles or furan in the presence of hydrogen chloride. Either heteroaromatic *N*-benzylhydroxylamines, symmetrical or unsymmetrical 2,2′-bis(heteroaryl)alkanes could be selectively produced depending on the experimental conditions.

The condensation of pyrrole derivatives with electrophiles allows the preparation of important synthetic intermediates for an access to natural alkaloids,[1] as well as other compounds of biological interest.[2] Among the various electrophiles, aldehydes have been considerably employed for the synthesis of porphyrins and their core-modified analogues.[3] Mannich reaction has also been widely described in order to prepare 2-aminomethylpyrroles.[4] However, the direct preparation of 2-*N*-hydroxyaminomethylpyrroles from a convenient electrophile has been mainly limited to the reaction between pyrrole and acyclic oxyiminium cations.[5]

Previous studies in our group have dealt with the reactivity of nitrones as electrophiles.[6] Among them, the reaction of nitrones with various indoles has been studied.[7] Two types of products have been obtained depending on the experimental conditions. Using chlorotrimethylsilane as a promoter, the exclusive formation of 3,3′-bis(indolyl)alkanes was observed, whereas when HCl was employed, 3-indolyl *N*-hydroxylamines were formed as single products.

In this letter, we describe the first example of a reaction between pyrroles or furan and nitrones in the presence of HCl as the activating agent providing either 2-heteroaromatic *N*-benzylhydroxylamines or 2,2′-bis(heteroaryl)alkanes concisely.

We started our work with the selective preparation of *N*-benzylhydroxylamines **3a**–**d**. 2,3,4-Trisubstituted pyrroles **1a** and **1b**[8] were used in order to limit the possible pyrrole polymerization under acidic conditions. Concerning the electrophilic partners, aldonitrones **2a** and **2b** have been chosen.[9] Experiments were performed using dry HCl in anhydrous methanol. Representative results are shown in Table 1 (Scheme 1).

Reactions with pyrrole derivative **1a** (with an acyl substituent) needed higher temperatures than reactions with pyrrole derivative **1b** which is indeed more electron-rich

Table 1. Selective preparation of 2-pyrrolyl *N*-hydroxylamines **3a**–**d**

Entry	Pyrrole	Nitrone	Conditions[a]	Ratio **3**:**4**	Yield (%)[b]
1	**1a**	**2a**	−20 °C, 2 h	100:0 (**3a**:**4a**)	20
2	**1a**	**2a**	−20 °C, 4 h	100:0 (**3a**:**4a**)	75
3	**1a**	**2a**	0 °C, 2 h	62:38 (**3a**:**4a**)	69
4	**1a**	**2b**	−40 °C, 2 h	100:0 (**3b**:**4b**)	15
5	**1a**	**2b**	−40 °C, 24 h	100:0 (**3b**:**4b**)	55
6	**1b**	**2a**	−78 °C, 3 h	100:0 (**3c**:**4c**)	66
7	**1b**	**2a**	−78 °C, 4.5 h	83:17 (**3c**:**4c**)	68
8	**1b**	**2b**	−78 °C, 3 h	100:0 (**3d**:**4d**)	41
9	**1b**	**2b**	−78 °C, 4.5 h	67:33 (**3d**:**4d**)	61

[a] In the presence of 1 equiv of HCl.
[b] Isolated yields.

Keywords: Nitrones; Pyrroles; Furan; Hydroxylamines; 2,2′-Bis-(heteroaryl)alkanes.
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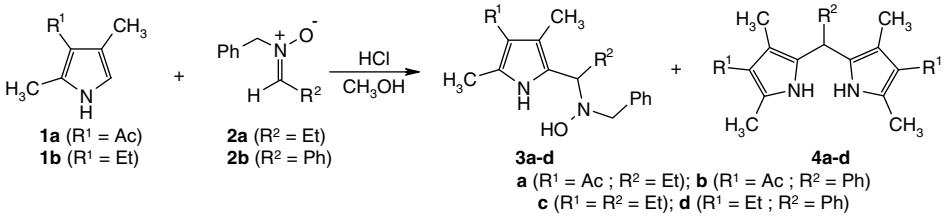


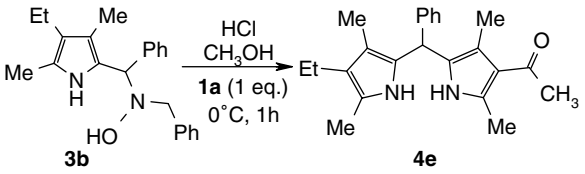
Scheme 1.

(with only alkyl substituents) (Table 1, entries 1–5 vs 6–9). In the case of **1a**, formation of small amounts of 2,2′-bis(pyrrolyl)alkane **4a** was observed when raising the temperature (Table 1, entries 1 vs 3). An increase in the reaction time improved the conversion to *N*-benzylhydroxylamines **3a**,**b** (Table 1, entries 1 vs 2 and 4 vs 5) while for **1b**, competitive formation of 2,2′-bis(pyrrolyl)alkanes **4c**,**d** occurred (Table 1, entries 6 vs 7 and 8 vs 9). For both pyrroles (**1a**,**b**), we found optimized experimental conditions leading to the exclusive formation of *N*-benzylhydroxylamines (**3a**–**d**; Table 1, entries 2, 5, 6, and 8).

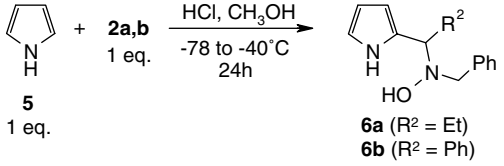
Furthermore, we took advantage of our initial observations in order to prepare 2,2′-bis(pyrrolyl)alkanes **4a**–**d** selectively via simple modifications of the experimental procedure. Our results are shown in Table 2. Highly selective transformations were observed here by increasing the relative amounts of pyrroles **1a**,**b** and HCl to 2 equiv (nitrone/pyrrole/HCl: 1/2/2) and by running the reactions at higher temperatures.

An efficient preparation of these compounds usually consists in reacting pyrroles and aldehydes under acidic conditions.[10] The assumed mechanism involves the formation of an intermediate carbinol which is rarely isolated.[11,12] In our case, elimination of *N*-benzylhydroxylamine from **3a**–**d** under acidic conditions followed by a second addition of pyrroles **1a**,**b** leads to compounds **4a**–**d**.[13] This hypothesis was confirmed by running a crossed reaction between *N*-hydroxylamine **3b** and 1 equiv of pyrrole **1a** in the presence of 1 equiv of HCl at 0 °C which gave unsymmetrical 2,2′-bis(pyrrolyl)alkane **4e** in 54% yield (Scheme 2).[14]

To summarize, we have found experimental conditions allowing selective access to either *N*-benzylhydroxylamines **3a**–**d** (Table 1), symmetrical 2,2′-bis(pyrrolyl)-



Scheme 2.



Scheme 3.

alkanes **4a**–**d** (Table 2), or unsymmetrical 2,2′-bis(pyrrolyl)alkane **4e** (Scheme 2) with fair to excellent yields.

Encouraged by these results, we decided to turn our attention to unsubstituted pyrrole (**5**), in order to prepare the corresponding *N*-benzylhydroxylamines **6a**,**b** (Scheme 3). Such compounds would be valuable for further ring functionalizations. Results are summarized in Table 3. As expected, the reaction always occurred selectively at the C-2 position of the pyrrole ring over 24 h at −40 °C.[15] Under this set of experimental conditions, polymerization of pyrrole (**5**) was minimal.

Formation of 2,2′-bis(pyrrolyl)alkanes was never detected, even under harsher experimental conditions. This was probably due to the faster degradation of both pyrrole (**5**) and hydroxylamines **6a**,**b** than a second addition step. Higher temperatures (Table 3, entries 2 vs 3, 4 vs 5 and 6) or a longer reaction time (65% in 36 h) afforded

Table 2. Selective preparation of 2,2′-bis(pyrrolyl)alkanes **4a**–**d**

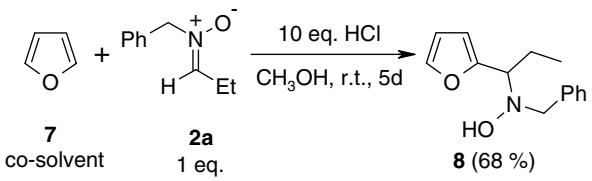
Entry	Pyrrole[a]	Nitrone	Conditions[b]	Ratio **3**:**4**	Yield (%)[c]
1	**1a**	**2a**	rt, 3 h	0:100 (**3a**:**4a**)	81
2	**1a**	**2b**	rt, 3.5 h	0:100 (**3b**:**4b**)	90
3	**1b**	**2a**	0 °C, 2 h	0:100 (**3c**:**4c**)	67
4	**1b**	**2b**	−78 °C, 4.5 h	36:64 (**3d**:**4d**)	55
5	**1b**	**2b**	rt, 1 h	0:100 (**3d**:**4d**)	77

[a] Two equivalents of pyrrole **1a**,**b** were used.
[b] In the presence of 2 equiv of HCl.
[c] Isolated yields.

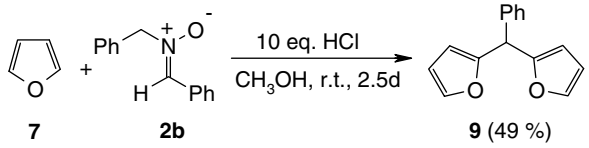
Table 3. Selective formation of hydroxylamines **6a**,**b**

Entry	Nitrone	Relative amount of HCl (equiv)	*N*-Benzylhydroxylamine **6** (yield %)[a]
1	**2a**	1	**6a** (65%)
2	**2a**	2	**6a** (95%)
3	**2a**	2[b]	**6a** (50%)[c]
4	**2b**	2	**6b** (73%)
5	**2b**	2[b]	**6b** (50%)
6	**2b**	2[d]	**6b** (32%)[c]

[a] Isolated yields.
[b] Pyrrole (**5**) was added at −40 °C.
[c] 35% of nitrone was recovered.
[d] Reaction was performed at −20 °C.



Scheme 4.



Scheme 5.

indeed products **6a**,**b** in lower yields. We also found that the use of 2 equiv of HCl was optimal (Table 3, entries 1 vs 2). By this way, 2-pyrrolyl *N*-benzylhydroxylamines **6a** and **6b** could be isolated in one step with good to excellent yields (Table 3, entries 2 and 4).

This study was then extended to furan (**7**). Under the previous conditions, no reaction was observed. However, significant results were obtained using furan as a cosolvent, by increasing the relative amount of HCl, at higher reaction temperature, and with a longer reaction time (Schemes 4 and 5). This weaker reactivity correlated well with some studies attributing a lower nucleophilicity to furan (**7**) than to pyrrole (**5**).[16] In the case of nitrone **2a**, we observed the formation of the 2-furyl *N*-benzylhydroxylamine **8** as a single product in 68% isolated yield (Scheme 4). As in the pyrrole series, reaction occurred only at the C-2 position. Interestingly, with nitrone **2b**, 2,2′-bis(furyl)alkane **9** was preferentially obtained (Scheme 5) in 49% yield (not optimized) under similar conditions.[17,18] This difference was probably due to the increased resonance stabilization of the possible intermediate 2-alkylidene-2*H*-furylium cation which could therefore easily react with a second equivalent of furan (**7**).

Finally, all attempts involving thiophene as the nucleophilic species under these experimental conditions were unsuccessful, either recovery or degradation of the starting material being observed.

In conclusion, we have shown that the reaction of nitrones with heteroaromatic compounds such as pyrrole or furan is an efficient, simple, and unprecedented method for the synthesis of 2-pyrrolyl[19a] and 2-furyl *N*-hydroxylamines.[20] The former molecules were never prepared so far, while the latter were previously obtained via addition of the corresponding 2-lithiofuran to nitrones.[21] They would be valuable building blocks for the elaboration of new drug candidates. Our method allows supplementary access to symmetrical 2,2′-bis(heteroaryl)alkanes.[19b] Furthermore, it represents a straightforward preparation of unsymmetrical 2,2′-bis(heteroaryl)alkanes.[14] Studies concerning new extensions of this methodology and applications to the synthesis of bioactive compounds are in progress.

Acknowledgement

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19. (a) *Typical experimental procedure for the preparation of N-benzylhydroxylamine* **6a**: Distilled acetyl chloride (157 mg; 2 mmol; 0.2–0.5 M in methanol) was added dropwise at 0 °C to anhydrous methanol (5 mL) in a 10 mL round-bottomed flask and the mixture was stirred for 15 min under argon. Nitrone **2a** (163 mg; 1 mmol) was then added and the mixture was cooled to −78 °C before the addition of pyrrole **5** (67 mg; 1 mmol). Reaction temperature was then set to −40 °C and stirring was continued until complete disappearance of starting material (followed by TLC with UV detection, alkaline $KMnO_4$ or TTC[22] staining). The mixture was treated with saturated aqueous $NaHCO_3$ solution until pH 8–9. The aqueous layer was then extracted with dichloromethane, the combined organic layers were washed with brine, and dried over anhydrous sodium sulfate. After filtration and evaporation of the solvents under vacuum, the crude product was purified by flash silica gel chromatography (pre-treated with 2.5% w/w of triethylamine; eluent: pentane/ethyl acetate: 8/2). Compound **6a** was isolated as a colorless oil (219 mg; 95% yield). IR (film): $\nu = 3454$, 3222, 3023, 2957, 2932, 2874, 1497, 1451, 1401, 1269 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.66$ (br s, 1H), 7.24–7.33 (m, 5H), 6.77–6.79 (m, 1H), 6.14–6.17 (m, 1H), 6.04 (br s, 1H), 5.89 (br s, 1H), 3.56 (dd, $J = 6.0$, 9.0 Hz, 1H), 3.55 (AB_q, $J_{AB} = 13.2$ Hz, $\delta_A - \delta_B = 45.2$ Hz, 2H), 1.82–1.96 (m, 1H), 1.67–1.80 (m, 1H), 0.88 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 137.9$, 129.8, 129.7, 128.2, 127.3, 117.6, 108.3, 107.2, 65.5, 60.2, 25.3, 11.4. MS (ESI) m/z (%) = 230.9 $[M+H]^+$ (20), 124.0 (100), 108.1 (68). Anal. Calcd (%) for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.16. Found (%): C, 72.63; H, 7.93; N, 11.98.; (b) *Typical experimental procedure for the preparation of 2,2′-bis(pyrrolyl)alkane* **4a**: Anhydrous acetyl chloride (157 mg; 2 mmol) was added dropwise at 0 °C to anhydrous methanol (5 mL) in a 10 mL round-bottomed flask and the mixture was stirred for 15 min under argon. Nitrone **2a** (163 mg; 1 mmol) and pyrrole **1a** (137 mg; 2 mmol) were then added at 0 °C. Stirring was continued for 3 h. Subsequent work-up procedure was performed as described above and purification by flash silica gel chromatography (pre-treated with 2.5% w/w of triethylamine; eluent: pentane/ethyl acetate: 6/4) led to pure **4a** as a white powder (129 mg; 81% yield). Mp 207–208 °C. IR (KBr): $\nu = 3301$, 3030, 2961, 2924, 2870, 1629, 1583, 1517, 1442, 1414, 1381, 1252 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.43$ (br s, 2H), 4.00 (t, $J = 7.3$ Hz, 1H), 2.42 (s, 6H), 2.41 (s, 6H), 2.22 (s, 6H), 1.89–1.99 (m, 2H), 0.89 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 196.8$, 134.9, 128.6, 121.1, 115.2, 33.7, 31.0, 27.2, 15.2, 12.4, 12.0. MS (DCI, NH_3+isobutane) m/z (%) = 315 $[MH^+]$ (63), 178 (100), 138 (63). Anal. Calcd (%) for $C_{19}H_{26}N_2O_2$: C, 72.58; H, 8.33; N, 8.91. Found (%): C, 72.36; H, 8.35; N, 8.52.
20. Compound **8**: Colorless oil. IR (film): $\nu = 3240$, 3034, 2967, 2926, 2870, 1498, 1455, 1324, 1152 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.43$–7.44 (m, 1H), 7.22–7.32 (m, 5H), 6.37–6.39 (m, 1H), 6.26–6.27 (m, 1H), 5.92 (br s, 1H), 3.62 (AB_q, $J_{AB} = 13.2$ Hz, $\delta_A - \delta_B = 46.1$ Hz, 2H), 3.60 (dd, $J = 5.7$, 9.3 Hz, 1H), 1.75–2.00 (m, 2H), 0.81 (t, $J = 7.5$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 153.1$, 141.9, 137.9, 129.7, 128.2, 127.2, 110.1, 109.1, 65.9, 60.7, 23.9, 11.0. MS (ESI, additive LiCl) m/z (%) = 237.9 $[M+Li]^+$ (20), 231.9 $[M+H]^+$ (22). Anal. Calcd (%) for $C_{14}H_{17}NO_2$: C, 72.71; H, 7.41; N, 6.06. Found (%): C, 72.53; H, 7.54; N, 5.95.
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