A New Synthetic Route to 1,3-Benzoxazepines

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A novel method for the synthesis of 5-hydroxy-1,3-benzoxazepines **5** utilizing the Staudinger reaction followed by an intramolecular aza-Wittig reaction, from *o*-acyloxyphenacyl azides **2** is reported.

In recent years, there has been a significant interest in the chemistry of iminophosphoranes (phosphazenes).[1] These compounds can be obtained by reaction of tertiary phosphines with organic azides as originally reported by Staudinger.[2] Iminophosphoranes are known to react with carbonyl compounds to give linear[3] or cyclic[4] imines, and this method has been used for the preparation of quinolines,[5] isoquinolines,[6] benzoxazoles,[7] pyrazines,[8] and triazoles.[9]

Continuing our studies on the synthesis of heterocyclic compounds,[10] we considered the reaction of *o*-acyloxyphenacyl azides **2** with triethyl phosphite as an entry to a new type of iminophosphoranes of potential utility in heterocyclic synthesis. We now describe a new method for the synthesis of the hitherto unknown 5-hydroxy-1,3-benzoxazepines **5** based upon the Staudinger reaction followed by an intramolecular aza-Wittig reaction of *o*-acyloxyphenacyl azides **2**. Two general methods for the preparation of 1,3-benzoxazepine ring system have been reported. The first method is based on the photo rearrangement of isoquinoline *N*-oxides,[11,12] whereas the second one involves the thermal rearrangement of azido chromenes.[13,14]

The starting compounds, *o*-acyloxyphenacyl azides **2b–d**, were obtained by treatment of *o*-hydroxyphenacyl azide **(1)**[15] with acid chlorides in the presence of triethylamine in tetrahydrofuran. On the other hand, **2a** was prepared by treatment of **1** with excess acetic formic anhydride in the presence of pyridine. The reaction of *o*-acyloxyphenacyl azides **2** with an equimolecular amount of triethyl phosphite in benzene at 5–10 °C for 0.5 h, and then heating to reflux temperature gave the desired 5-hydroxy-1,3-benzoxazepines **5** in yields ranging from 30 to 74%. The isolation of iminophosphoranes **3** was unsuccessful[8] under various reaction conditions.

The formation of the cyclization products **5** can be assumed to proceed via the expected phosphorane intermediate **3** with the evolution of nitrogen followed by an intramolecular aza-Wittig reaction between phosphorane and ester carbonyl group, followed by spontaneous tautomerization. This assumption may be supported by the isolation of the rearrangement product, *N*-(*o*-hydroxyphenacyl)benzamide **(6)**, when the reaction of *o*-benzoyloxyphenacyl azide **(2d)** with triethyl phosphite was carried out. Similar rearrangement pathway has been reported[16] in the reaction of *o*-azidophenyl benzoate with hexamethylphosphoric triamide.

Structural elucidation of **5** is accomplished on the basis of spectral data[11] and microanalyses. The IR spectra show absorption in the OH stretching region of ν = 3047–3085 cm^{-1}. The ^{1}H-NMR spectra of **5** are also consistent with the structure assigned. These values are in

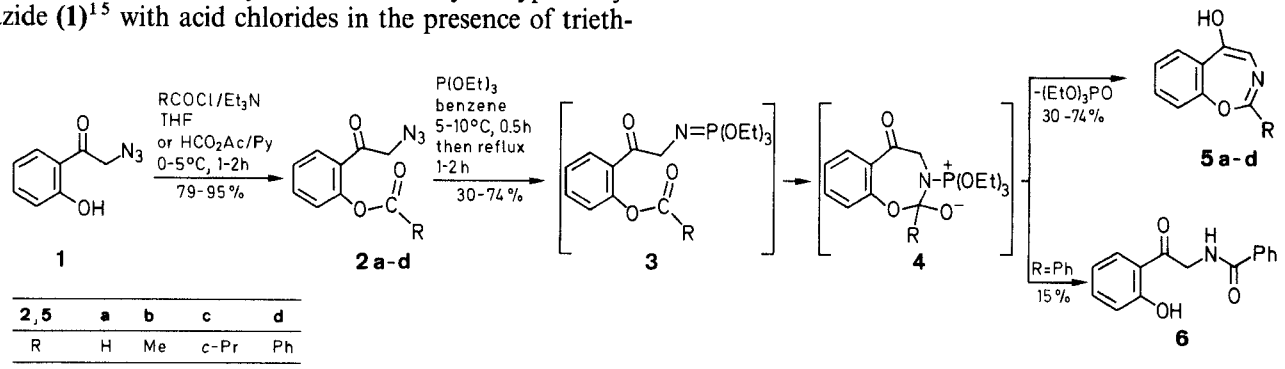

Table 1. *o*-Acyloxyphenacyl Azides **2** Prepared

Product	Reaction Time (h)	Yield[a] (%)	mp (°C)[b]	Molecular Formula[c]	^{1}H-NMR ($CDCl_3$/TMS) δ, J(Hz)
2a	2	91	oil	$C_9H_7N_3O_3$ (205.2)	4.43 (s, 2H, CH_2), 7.10–7.93 (m, 4H_{arom}), 8.33 (s, 1H, CHO)
2b	1	95	54–55	$C_{10}H_9N_3O_3$ (219.2)	2.33 (s, 3H, CH_3), 4.40 (s, 2H, CH_2), 7.07–7.87 (m, 4H_{arom})
2c	1	79	50–51	$C_{12}H_{11}N_3O_3$ (245.2)	1.17 (m, 4H, CH_2-cyclopropyl), 1.82 (m, 1H, CH-cyclopropyl), 4.36 (s, 2H, CH_2), 7.03–7.83 (m, 4H_{arom})
2d	1.5	90	59–60	$C_{15}H_{11}N_3O_3$ (281.3)	4.36 (s, 2H, CH_2), 7.17–8.33 (m, 9H_{arom})

[a] Yield of pure isolated product, except **2a**.
[b] Recrystallized from Et_2O/petroleum ether.
[c] Satisfactory microanalyses obtained: C ±0.28, H ±0.07, N ±0.30, except for **2a**, which could not be purified.

Table 2. 5-Hydroxy-1,3-benzoxazepines **5** Prepared

Product	Reaction Time (h)	Yield[a] (%)	mp (°C) (solvent)	Molecular Formula[b]	IR (KBr) ν_{OH} (cm^{-1})	^{1}H-NMR (DMSO-d_6 + $CDCl_3$/TMS) δ, J (Hz)	MS (70 eV) m/z (%)
5a	2	30	157–158 (Et_2O)	$C_9H_7NO_2$ (161.2)	3047	6.86–7.19 (m, 3 H_{arom}), 7.60 (s, 1 H, H-4), 7.68 (m, 1 H_{arom}), 7.98 (s, 1 H, H-2), 9.92 (s, 1 H, OH)	161 (M^+, 21), 134 (29), 133 (22), 106 (13), 105 (100), 104 (29), 78 (42), 77 (45), 76 (23), 65 (19), 63 (22)
5b	2	74	160–161 (Et_2O)	$C_{10}H_9NO_2$ (175.2)	3050	2.47 (s, 3 H, CH_3), 6.86–7.29 (m, 3 H_{arom}), 7.45 (s, 1 H, H-4), 7.57 (m, 1 H_{arom}), 10.33 (s, 1 H, OH)	175 (M^+, 43), 134 (29), 133 (15), 105 (100), 104 (15), 91 (13), 78 (19), 77 (31), 76 (13), 65 (15), 63 (12)
5c	1	68	181–182 (Et_2O)	$C_{12}H_{11}NO_2$ (201.2)	3059	1.05 (m, 4 H, CH_2-cyclopropyl), 2.11 (m, 1 H, CH-cyclopropyl), 6.83–7.14 (m, 3 H_{arom}), 7.41 (s, 1 H, H-4), 7.59 (m, 1 H_{arom}), 9.94 (s, 1 H, OH)	201 (M^+, 67), 172 (14), 134 (38), 133 (14), 131 (37), 121 (18), 105 (100), 104 (18), 78 (13), 77 (28), 76 (10), 65 (20), 63 (10)
5d	1	39	251–252 (Et_2O/ EtOAc)	$C_{15}H_{11}NO_2$ (237.3)	3085	6.90–7.21, 7.48–7.54 (m, 6 H_{arom}), 7.67 (s, 1 H, H-4), 7.80, 8.10 (m, 3 H_{arom}), 10.19 (s, 1 H, OH)	237 (M^+, 58), 181 (37), 134 (49), 105 (100), 104 (14), 89 (27), 78 (13), 77 (54), 76 (23), 65 (21), 63 (27)

[a] Yield of isolated pure product. Low yield **5a** presumably due to the instability of **2a**.
[b] Satisfactory microanalyses obtained: C ±0.32, H ±0.27, N ±0.31.

good agreement with those reported for the similar system.[13] In the NMR spectrum of **5b** the signal at $\delta = 10.33$ (OH) disappeared by addition of deuterium oxide. All compounds show a molecular ion and peaks due to the loss of RCN from the molecular ion, then further the expulsion of carbon monoxide. The most intense peaks in the spectra of **5** occur at $m/z = 105$ and corresponds to the benzoyl radical ion.

We have thus worked out a useful and simple method for the synthesis of 5-hydroxy-1,3-benzoxazepines **5**, which are not easily obtainable by other routes.

Dry N_2 gas was routinely employed as the reaction atmosphere in all reactions. Benzene and THF were dried and distilled from Na and $LiAlH_4$, respectively. Silica gel EM 7747 for column chromatography was used throughout for product separation. Melting points were taken using an Electrothermal melting point apparatus and are uncorrected. Microanalyses were obtained using a Perkin-Elmer 240 DS element analyzer. Mass spectra were obtained using a Hewlett Packard model 5985 B spectrometer. IR spectra were recorded on a Analect FX 6160 IR spectrophotometer. ^{1}H-NMR spectra were measured on either a Bruker AM-200 (**5a–d**) or a Varian EM-360 A spectrometer (**2a–d**).

α-Hydroxyphenacyl azide (**1**)[15] and acetic formic anhydride[17] were prepared following literature procedures.

o-Formyloxyphenacyl Azide (2a):
To a stirred solution of *o*-hydroxyphenacyl azide (**1**; 1.77 g, 10 mmol) in excess acetic formic anhydride (30 mL) is added dropwise pyridine (0.97 g, 12.3 mmol) at 0–5 °C. After stirring for 2 h at r.t. the mixture is poured into cold water (200 mL), and extracted with CH_2Cl_2 (3 × 50 mL). The extract is dried ($MgSO_4$), and the solvent is evaporated under reduced pressure to give **2a** as a light yellow oil, which is subjected to the next reaction without further purification;[18] yield: 1.86 g (91 %).

o-Acyloxyphenacyl Azides 2b–d; General Procedure:
To a stirred solution of *o*-hydroxyphenacyl azide (**1**; 1.77 g, 10 mmol) in THF (20 mL) is added dropwise Et_3N (1.11 g, 11 mmol) and the acid chloride (10.5 mmol) at 0–5 °C. After stirring for the time indicated in Table 1 at r.t., the precipitated solid ($Et_3N \cdot HCl$) is filtered, and the filtrate is concentrated under reduced pressure. The residual oil is purified by short-column chromatography on silica gel (hexane/EtOAc, 10:1) to give **2b–d**.

5-Hydroxy-1,3-benzoxazepines 5; General Procedure:
To a stirred solution of the appropriate *o*-acyloxyphenacyl azide **2** (10 mmol) in benzene (30 mL) is added slowly $P(OEt)_3$ (1.66 g, 10 mmol) at 5–10 °C. The mixture is stirred for 0.5 h at r.t., and then refluxed for the time indicated in Table 2. The mixture is concentrated under reduced pressure, and the residual material is chromatographed on a silica gel column (hexane/EtOAc, 1:1) to give **5** as colorless crystals. An analytical sample is prepared by recrystallization from the appropriate solvent (Table 2).

In the case of the reaction of **2d** with $P(OEt)_3$, the rearrangement product, *N*-(2-hydroxyphenacyl)benzamide (**6**) is also isolated; yield: 15 %; mp 148–149 °C (EtOAc/Et_2O).

6:

$C_{15}H_{13}NO_3$ (255.3) calc. C 70.58 H 5.13 N 5.49
found 70.86 5.23 5.15

^{1}H-NMR (DMSO-d_6/TMS): $\delta = 4.81$ (d, 2 H, $J = 5.66$ Hz, CH_2), 7.01, 7.52, 7.94 (m, 9 H_{arom}), 8.85 (t, 1 H, $J = 5.62$ Hz, NH), 11,39 (s, 1 H, OH).

MS (70 eV): $m/z = 255$ (M^+), 121, 105, 93, 77, 65, 51.

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