# Synthesis of 3-Substituted 1*H*-1,2-Benzodiazepines

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Although 1*H*-1,2-benzodiazepines are receiving some attention, few synthetic methods are available for their preparation and only a few 3-substituted derivatives have been hitherto reported[1-4]. In view of a potential interest for this class of compounds in pharmacology, we have developed a general procedure for the synthesis of 1*H*-1,2-benzodiazepines bearing an electron-withdrawing substituent in the 3-position.

Diazotization of amine **1** followed by coupling with the α-chlorocarbonyl compounds **3a–e** gave the hydrazonyl chlorides **4a–e**, which were dehydrated to the corresponding olefinic compounds **5a–e** on treatment with phosphorus pentoxide. The latter intermediates reacted with an excess of triethylamine in boiling benzene to afford the desired 1*H*-1,2-benzodiazepines **7a–e**. Reaction times, yields, and physical and spectral data are given in Tables 1 and 2.

It is apparent from these results that the formation of **7**, which can be interpreted as an electrocyclic reaction of the transient nitrile imine intermediates **6**, represents a general process occurring with different substituents at the electron-deficient end of the 1,3-dipolar function. However, this synthetic procedure cannot be adopted to obtain 1*H*-1,2-

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benzodiazepines with electron-donating groups in the 3-position; in fact, this type of substitution precludes the coupling reaction between **2** and **3**.

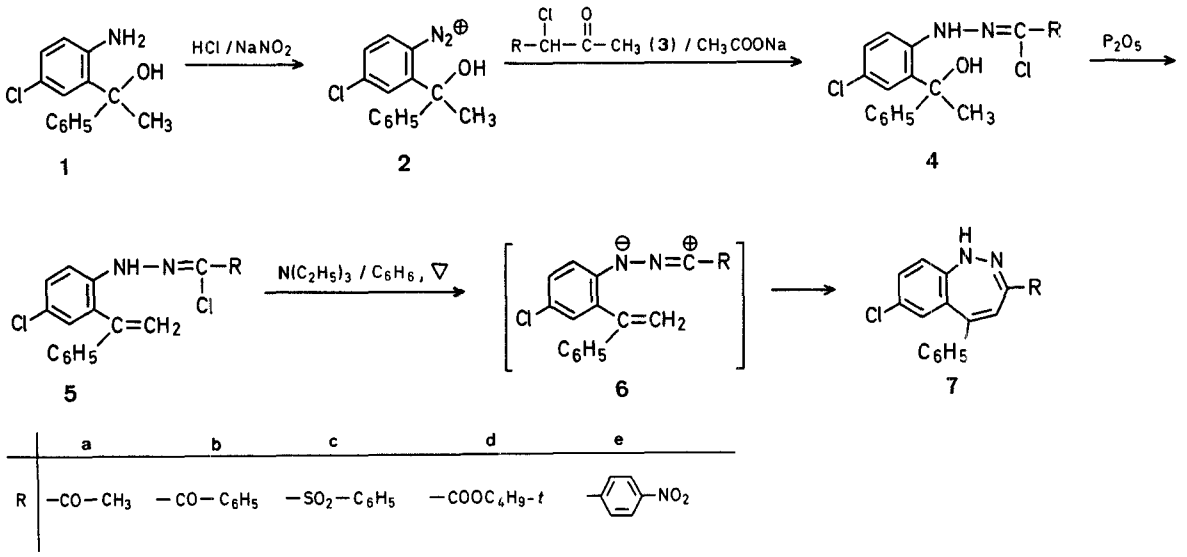


**Table 1.** Preparation of Intermediates **4** and **5**

| Compound | Yield [%] | m.p.[a,b] | Empirical formula[c] |
|---|---|---|---|
| **4a** | 40 | 149–150° | $C_{17}H_{16}Cl_2N_2O_2$ (351.2) |
| **4b** | 43 | 153–155° | $C_{22}H_{18}Cl_2N_2O_2$ (413.3) |
| **4c** | 36 | 136–138° | $C_{21}H_{18}Cl_2N_2O_3S$ (449.3) |
| **4d** | 55 | 167–168° (dec.) | $C_{20}H_{22}Cl_2N_2O_3$ (409.3) |
| **4e** | 27 | 151–153° | $C_{21}H_{17}Cl_2N_3O_3$ (430.3) |
| **5a** | 78 | 90–91° | $C_{17}H_{14}Cl_2N_2O$ (333.2) |
| **5b** | 85 | 108–110° | $C_{22}H_{16}Cl_2N_2O$ (395.3) |
| **5c** | 85 | oil[d] | — |
| **5d** | 24 | 124–125° | $C_{20}H_{20}Cl_2N_2O_2$ (391.3) |
| **5e** | 84 | 127–129° | $C_{21}H_{15}Cl_2N_3O_2$ (412.3) |

[a] Uncorrected.
[b] Recrystallization solvent: diisopropyl ether/ethanol for **4**, diethyl ether/light petroleum for **5**.
[c] Satisfactory microanalyses (C ±0.22%, H ±0.11%, N ±0.22%) were obtained with exception of compound **5c**.
[d] Purity better than 95% as determined by $^1$H-N.M.R. analysis.

**1-Chloro-1-phenylsulfonyl-2-propanone (3c):**
A solution of sulfuryl chloride (2.7 g) in dry chloroform (10 ml) is added over 2 h to a solution of phenylsulfonylacetone (3.0 g) in dry chloroform (10 ml) under cooling at 0°. After 2 h standing at room temperature, the solvent is removed under reduced pressure to afford crude **3c** as a viscous oil; yield: 2.8 g.

$^1$H-N.M.R. ($CDCl_3$): $\delta$ = 2.52 (s, 3H); 5.18 (s, 1H); 7.5–8.1 ppm (m, 5H).

Preparations of compounds **3a**[5], **3b**[6], **3d**[7], and **3e**[8] have been described in the chemical literature.

**Preparation of Hydrazonyl Chlorides 4; General Procedure:**
A solution of sodium nitrite (20 mmol) in water (10 ml) is added to a solution of amine **1**[9] (20 mmol) in 0.5 normal hydrochloric acid (125 ml) under stirring and ice-cooling. The solution is then adjusted to pH 4 with sodium acetate and a solution of **3** (20 mmol) in methanol (10 ml) is added dropwise at 0–5° under vigorous stirring. After 3 h stirring at room temperature, the mixture is extracted with ether, the organic solution is dried with sodium sulfate, and evaporated. The residue is chromatographed on a silica gel column (diethyl ether/light petroleum 1:1 as eluent) to give **4**. See Table 1.

**Preparation of Hydrazonyl Chlorides 5; General Procedure:**
A solution of **4** (12 mmol) in dry benzene (150 ml) is treated with phosphorus pentoxide (42 mmol) and stirred overnight at room

**Table 2.** Preparation of 1*H*-1,2-Benzodiazepines (**7**)

| Compound | Reaction time [h] | Yield [%] | m.p.[a,b,c] | Empirical formula[d] | I.R. (nujol) $\nu$ [cm$^{-1}$] | $^1$H-N.M.R. ($CD_3COCD_3$) $\delta$ [ppm][e] |
|---|---|---|---|---|---|---|
| **7a** | 12 | 62 | 140° | $C_{17}H_{13}ClN_2O$ (296.7) | 3330, 1690 | 2.28 (s, 3H); 6.58 (d, 1H, $J$ = 2 Hz); 6.62 (s, 1H); 6.9–7.6 (m, 7H); 8.3 (broad s, 1H) |
| **7b** | 3 | 81 | 168° | $C_{22}H_{15}ClN_2O$ (358.8) | 3330, 1670 | 6.64 (d, 1H, $J$ = 2 Hz); 6.76 (s, 1H); 6.9–8.0 (m, 12H); 8.3 (broad s, 1H) |
| **7c** | 3 | 54 | 135° | $C_{21}H_{15}ClN_2O_2S$ (394.8) | 3340 | 6.60 (d, 1H, $J$ = 2 Hz); 6.62 (s, 1H); 6.9–8.1 (m, 12H); 8.5 (broad s, 1H) |
| **7d** | 13 | 79 | 195° (dec.) | $C_{20}H_{19}ClN_2O_2$ (354.8) | 3320, 1715 | 1.50 (s, 9H); 6.63 (d, 1H, $J$ = 2 Hz); 6.66 (s, 1H); 6.9–7.6 (m, 7H); 8.2 (broad s, 1H) |
| **7e** | 6 | 55 | 158° | $C_{21}H_{14}ClN_3O_2$ (375.8) | 3340 | 6.74 (d, 1H, $J$ = 2 Hz); 6.87 (s, 1H); 7.0–7.5 (m, 7H); 8.0–8.3 (overlapping signals, 5H) |

[a] Uncorrected.
[b] Orange-red or red crystals.
[c] From diisopropyl ether.
[d] All compounds gave correct microanalyses (C ±0.19%, H ±0.18%, N ±0.12%).
[e] Recorded on a Varian HA-100 instrument with TMS as an internal standard.

temperature. The mixture is poured into ice and the organic layer is washed with sodium hydrogen carbonate, dried with sodium sulfate, and evaporated. Recrystallization of the residue affords **5**. See Table 1. In the case of **4d**, the phosphorus pentoxide is filtered off and the solution is chromatographed on a silica gel column (benzene as eluent) to give **5d**. See Table 1.

**Preparation of 1*H*-1,2-Benzodiazepines (7); General Procedure:** A solution of **5** (5 mmol) and triethylamine (25 mmol) in dry benzene (250 ml) is refluxed for the time given in Table 2. The mixture is then washed with water, dried with sodium sulfate, and evaporated. Recrystallization of the residue affords **7**. See Table 2.

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