# Trifluoromethyl-substituted Dehydrodiazepines and Cyanopyrroles from Azido-/Tetrazolo-pyridines

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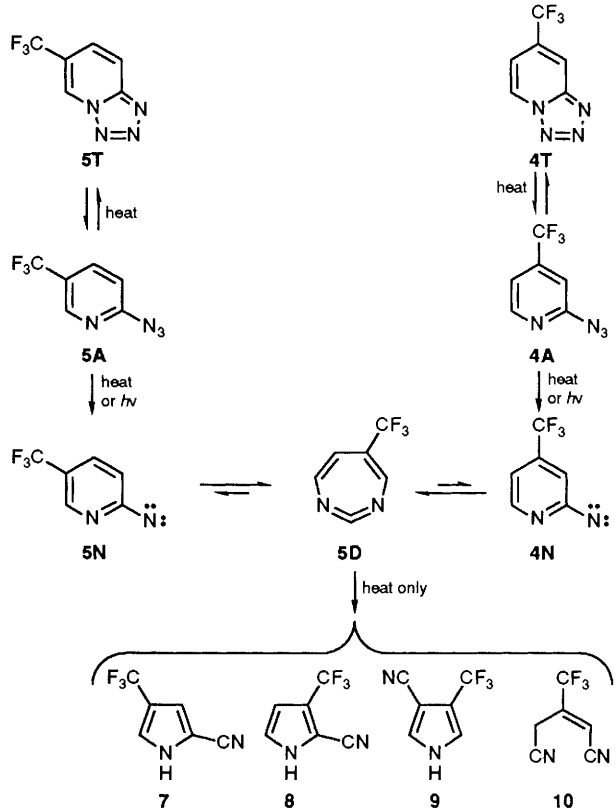
1,2-Didehydro-1,3-diazepines **4D**, **5D**, **4,6D** and **5,6D** are identified as unique products of both photolysis and thermolysis of azido-/tetrazolo-pyridines; the ultimate thermolysis products are trifluoromethylpyrrolecarbonitriles (**7–9**, **11–13** and **16–18**).

The thermal and photochemical ring expansion of 2-pyridylnitrenes[1,2] can in principle be used to synthesise 1,3-diazepine derivatives,[3] but the reaction has found little use, mainly because the starting materials, tetrazolo[1,5-*a*]pyridines, do not photolyse well under ordinary reaction conditions.

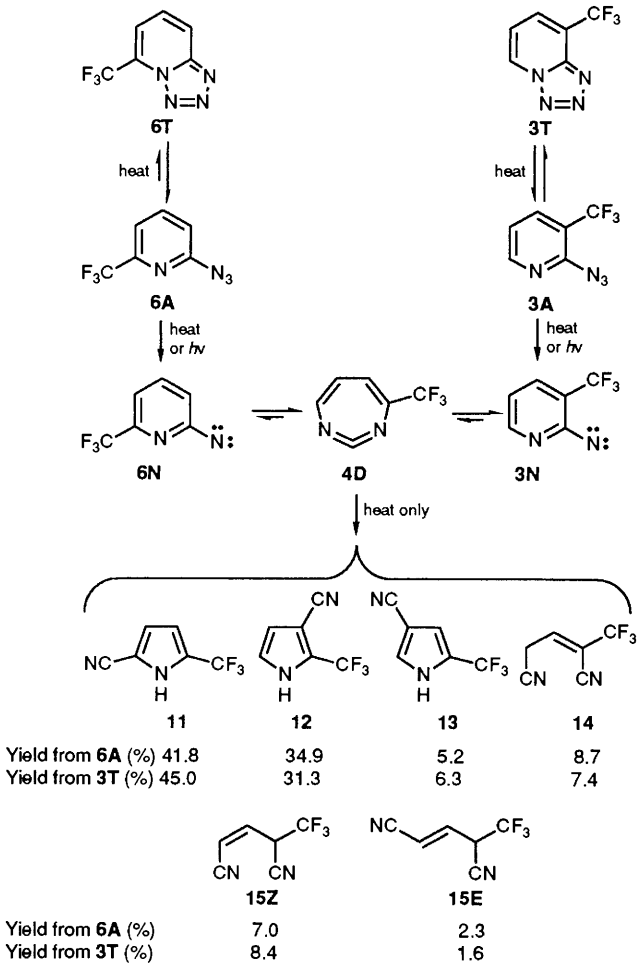
We report here a study of trifluoromethyl-substituted 2-pyridylnitrene precursors that photolyse very efficiently to 1,2-didehydro-1,3-diazepines (1,3-diazacyclohepta-1,2,4,6-tetraenes) (**4D**, **5D**, **4,6D** and **5,6D**).† We demonstrate the formation of distinct dehydrodiazepines linking different sets of 2-pyridylnitrenes (Schemes 1–3) under both photochemical and thermal conditions. The $CF_3$ group was chosen because of its proven pharmaceutical importance[4] and because of its electron-withdrawing effect which, as shown below, facilitates tetrazole–azide isomerism and increases nitrene reactivity. Furthermore, the reluctance of the $CF_3$ group to undergo migration guarantees the uniqueness of the novel cyano(trifluoromethyl)pyrroles obtained as final thermal reaction products (Schemes 1–3).

The tetrazole or azide starting materials were synthesised from the appropriate 2-chloropyridines by two methods, (*i*) direct nucleophilic substitution by $NaN_3$ in dimethylformamide (DMF) at 70 °C (**4T**, **5T**, **3T**, **6A**, **3,5T** and **4,5T**) and (*ii*) two-step reaction by diazotization of 2-hydrazinopyridines, obtained from the 2-chloropyridines with hydrazine hydrate in ethanol (reflux, 2–3 h) (**4T**, **5T**, **3T**, **6A** and **4,6A**). The yields




**Scheme 1** Relative yields of products are given

† Formulae are numbered according to the following system: **4A** is 4-trifluoromethyl-2-azidopyridine, **4T** is the corresponding tetrazolo[1,5-*a*]pyridine, and **4N** is the corresponding 2-pyridylnitrene; **5D** is 5-trifluoromethyl-1,2-didehydro-1,3-diazepine, *etc.*



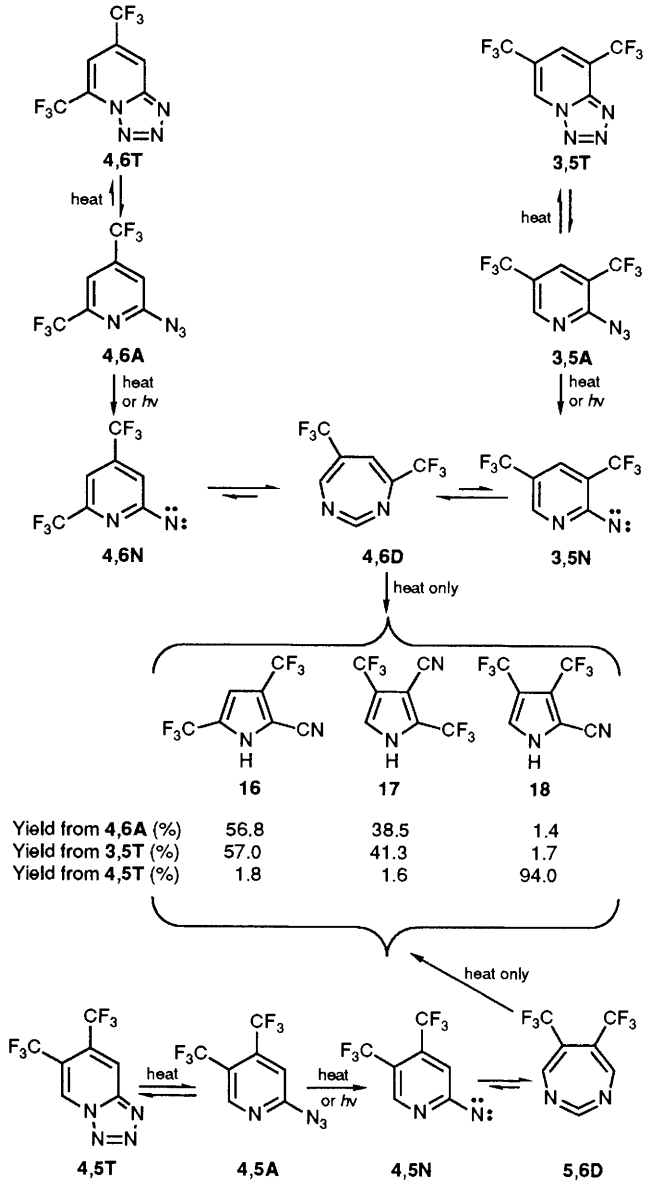

**Scheme 2** Relative yields of products are given

were 30–60%.‡ The tetrazole–azide valence tautomerisms were investigated by $^1H$ and $^{13}C$ NMR spectroscopy in $CDCl_3$, $(CD_3)_2SO$ and $CF_3CO_2D$ solution, and by IR spectroscopy in KBr, $Me_2SO$ and $CHCl_3$. Compounds **6A** and **4,6A** exist as azides in the pure liquid state at room temperature. However, all these azide-to-tetrazole isomerisations are exothermic ($\Delta H^\circ_{isom}$ = −13 to −30 kJ mol$^{-1}$) as determined by variable temperature $^1H$ NMR spectroscopy, thus implying that the existence of azides is an entropic effect; that this is indeed the case is revealed in the magnitude of $\Delta S^\circ_{isom}$ (−50 to −59 ± 8 J mol$^{-1}$ K$^{-1}$). Simple sublimation, usually at 40–50 °C caused significant ring opening of tetrazoles to azides in most cases.

Photolysis (unfiltered; high-presure Xe–Hg lamp; 12–18 K; 2–20 min) of the Ar matrix isolated azide–tetrazole mixtures in each case caused the rapid disappearance of the azides and tetrazoles and formation of new products absorbing strongly in the carbodiimide region in the IR spectra and therefore assigned as the dehydrodiazepines **4D, 5D, 4,6D** and **5,6D** (Schemes 1–3).‡

It is particularly noteworthy that *the same* dehydrodiazepine (**5D**) is formed from the isomeric tetrazoles **5T** and **4T**

‡ Correct microanalytical data (C,H,N) were obtained for **3T, 4T, 5T, 3,5T** and **4,5T** and correct high resolution mass spectra for **6A** and **7–18**. $^1H$ and $^{13}C$ NMR spectra are available for all tetrazoles, azides, pyrroles and pentenedinitriles. FTIR spectra of dehydrodiazepines (Ar matrix, 12–18 K) **4D** ν/cm$^{-1}$: 1992s, 1319m, 1294m, 1192s, 1164vs ($\nu_{CF}$), 1040m and 1006w; **5D** ν/cm$^{-1}$: 1997s, 1311m, 1184m, 1143s ($\nu_{CF}$) and 985m; **4,6D** ν/cm$^{-1}$: 2000s, 1279s, 1277s, 1200s, 1190w, 1186m, 1171s, 1151m (this and four preceding due to $\nu_{CF}$), 1041m and 985w; **5,6D** ν/cm$^{-1}$: 2010m, 1336s, 1307s, 1183s, 1167s ($\nu_{CF}$), 991m, 970w and 875w.




**Scheme 3** Relative yields of products are given

(Scheme 1); likewise, one, and only one dehydrodiazepine **4D** is formed from **3T** and **6A** (Scheme 2), and these two dehydrodiazepines (**5D** and **4D**) are different from each other, as demonstrated by their FTIR spectra. Similarly, two different bis(trifluoromethyl)dehydrodiazepines were formed from the three different precursors shown in Scheme 3.‡

The ring opening and ring expansion reactions also occurred under flash vacuum pyrolysis (FVP) conditions as monitored by FTIR spectroscopy of the products isolated neat (*ca.* −196 °C) or in Ar matrix (*ca.* 20 K). Complete ring opening of tetrazoles to azides occurred at 200–250 °C/10$^{-4}$ mbar. Formation of dehydrodiazepines occurred at 360–410 °C/10$^{-4}$ mbar and the identities of **4D** and **5D** with those obtained photochemically were confirmed by Ar matrix isolation. In separate experiments it was shown by Ar matrix ESR spectroscopy of the products of FVP at 400 °C that nitrenes were formed and survived the pyrolysis conditions, giving rise to strong signals near 730 mT.[5]

At FVP temperatures above 450 °C the dehydrodiazepines disappeared (gradually) and nitriles were formed in their place. The products of the preparative pyrolyses at 520 °C/10$^{-3}$ mbar were analysed by $^1H$ and $^{13}C$ NMR, GC–mass, high resolution mass and IR spectroscopy.‡ The results are given in Schemes 1–3 (relative yields of **7–18** by $^1H$ NMR and/or GC).

The mechanism of ring contraction[1,6] will be discussed elsewhere, but it is noteworthy that unique sets of products are formed from each set of starting materials, and there is little or no cross-over in products between reactions involving different nitrenes or dehydrodiazepines. This is due to the fact that almost no products of $CF_3$ group migration are formed; only the minor compound **18** from **4,6A** and **3,5T** and compounds **16** and **17** from **4,5T** (Scheme 3) necessitate such migration. To our knowledge, no other routes to cyano(trifluoromethyl)pyrroles are known. The present FVP reactions offer relatively easy access, particularly to the bis(trifluoromethyl)cyanopyrroles. The isolated yield of **18** from **4,5T** was 72%.

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