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Azolyl Substituted Tröger's Bases

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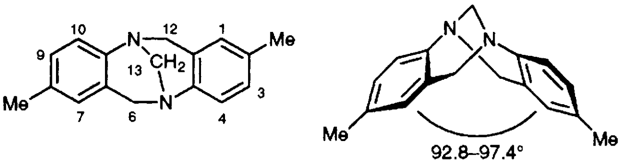
Tröger's bases **2**, **3** and **4** containing azole rings as substituents on the aromatic moiety have been synthesized for the first time.

Tröger's base **1** (2,8-dimethyl-5,11-methano-5,6,11,12-tetrahydrodibenzo[*b*,*f*][1,5]diazocine), first synthesized by Tröger in 1887,[1] is a concave chiral molecule. Prelog resolved it using chiral chromatography,[2] and more recently the resolution was carried out *via* diastereoisomeric salt formation.[3]

Tröger's base analogues provide relatively rigid chiral frameworks for the construction of chelating and biomimetic systems.[4] One limitation in the synthesis of such compounds has been the inability to prepare Tröger's bases with a wide variety of functional groups; for instance, Tröger's bases with electron withdrawing groups on the aromatic rings cannot be prepared.[5]

The only example of a Tröger's base analogue incorporating a heterocyclic substituent in its skeleton is a phenanthroline derivative which was shown to interact with DNA.[4f] In this note we describe the synthesis of the first Tröger's bases containing azole rings as substituents on the aromatic moiety, **2**, **3** and **4**, which could be used as hosts for hydrogen bond donor compounds and as ligands in coordination chemistry. Moreover, base **3** (a C-linked azole derivative), after removing the benzhydryl group, should show the complexing properties of azolate anions.

Compound **2** is the first example of the direct synthesis of a Tröger's base with two electron withdrawing groups (imidazol-1-yl is similar to chlorine in its electronic properties).[6] This compound was prepared (Scheme 1) from *N*-*p*-amino-



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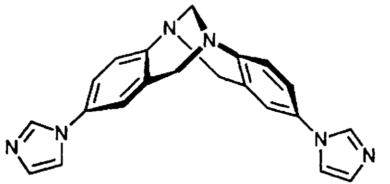

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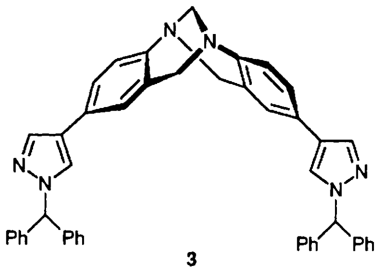

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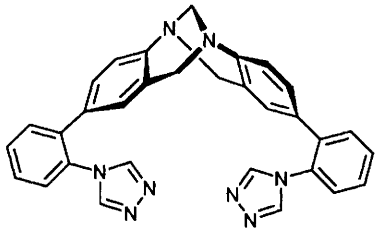

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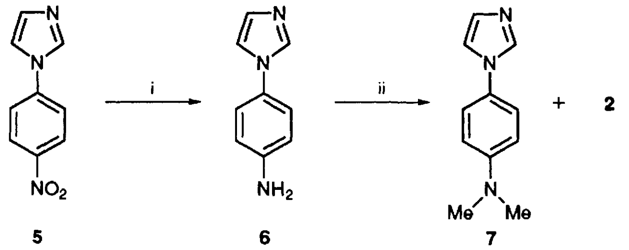
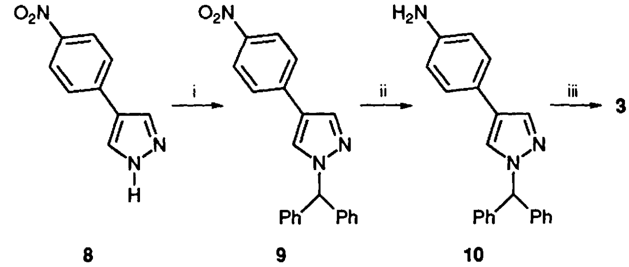
Table 1 Characteristics of the Tröger's bases[a]

				^{1}H NMR in CDCl$_3$ (δ, *J*/Hz)			
Tröger's base	M.p. *t*/°C	Yield (%)	$M^{+\bullet}$	6-H *endo*	13-H	6-H *exo*	$J_{exo,\ endo}$
2	230–232	30	354.435	4.25	4.36	4.78	17.1
3	190–192	60	686.881	4.15	4.32	4.67	16.8
4	272–274	30	508.613	4.04	4.30	4.61	16.5

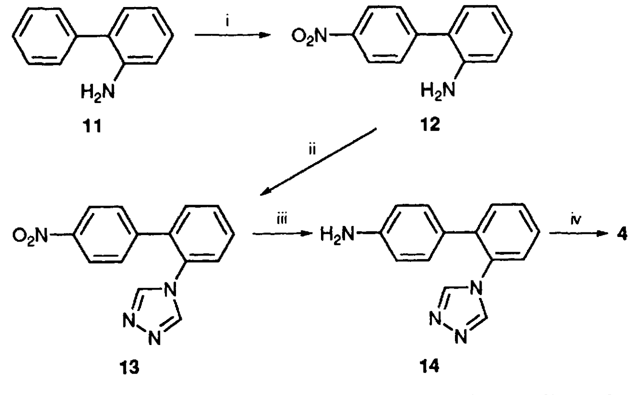
[a] Both ^{1}H and ^{13}C NMR spectra of compounds **2**–**4** have been carefully assigned by comparison with compound **1** and HETCOR and NOE experiments.



Scheme 1 *Reagents and conditions*: i, H_2, 10% Pd/C, ethanol, room temp., (**6**, 100%); ii, CH_2O, H_2O, 35% HCl, ethanol, 60 °C (**2**, 30%)



Scheme 2 *Reagents and conditions*: i, Ph_2CHCl, Na_2CO_3, KOH, $Bu_4N^+ Br^-$, xylene, reflux (**9**, 70%); ii, H_2, 10% Pd/C, ethanol, room temp., (**10**, 100%); iii, hexamethylenetetramine, trifluoroacetic acid, room temp. (**3**, 60%)



Scheme 3 *Reagents and conditions*: i, fuming HNO_3 (d = 1.52) H_2SO_4, 0 °C (**12**, 70%); ii, $(Me_2N\text{-}CH{=}N)_2$ toluene, toluene-*p*-sulfonic acid, reflux (**13**, 45%); iii, H_2 10%; Pd/C, ethanol, room temp. (**14**, 100%); iv, CH_2O, H_2O, 35% HCl, ethanol, 60 °C (**4**, 30%)

phenylimidazole **6** which, in turn, was obtained by catalytic hydrogenation of the corresponding nitro derivative **5**.[7] The reaction of the amine **6** with aqueous formaldehyde and concentrated hydrochloric acid afforded a mixture of **2** and **7**, the *N*,*N*-dimethyl derivative of **6**, in a 1 : 1 ratio. From this mixture, **2** was isolated in 30% yield by flash chromatography.

The conversion of **6** into **2** is very dependent on the proportion of hydrochloric acid. Thus, low proportions increase the formation of **7** and high proportions lead to complex reaction mixtures. The use of paraformaldehyde or hexamethylenetetramine instead of aqueous formaldehyde yields mixtures with the same or lower ratios of **2** to **7**.

In Scheme 2 the synthesis of base **3** from 4-*p*-nitrophenylpyrazole **8** is represented.[8] We have established that anilines bearing azoles unsubstituted on the nitrogen do not yield Tröger's bases but complex mixtures from which the desired base was absent. For this reason, the N–H was protected as the benzhydryl derivative **9**.[9] Subsequent hydrogenation led to the amine **10**, which was transformed into base **3** by reaction with hexamethylenetetramine and trifluoroacetic acid[10] in 60% yield.

Finally, base **4** was prepared from commercially available 2-aminobiphenyl **11** in the four-step procedure illustrated in Scheme 3. Nitration of compound **11** afforded the 4′-nitro derivative **12**,[11] which was transformed into the triazole **13** using a modification of Bartlett's method.[12] Catalytic hydrogenation of **13** yielded the amine **14** which when reacted with aqueous formaldehyde and the optimal quantity of hydrochloric acid yielded 30% of Tröger's base **4**. The use of a less acidic medium led to complex mixtures.

Bases **2**, **3** and **4**, all pale-yellow solids, were unambiguously characterized (see Table 1) by a combination of analytical (accurate mass spectrometry) and spectroscopic methods (^1H and ^{13}C NMR).†

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References

1 J. Tröger, *J. Prakt. Chem.*, 1877, **36**, 225.
2 V. Prelog and P. Wieland, *Helv. Chim. Acta*, 1944, **27**, 1127.
3 S. H. Wilen, J. Z. Qui and P. G. Williard, *J. Org. Chem.*, 1991, **56**, 485.
4 (*a*) C. S. Wilcox, *Tetrahedron Lett.*, 1985, **26**, 5749; (*b*) C. S. Wilcox and M. D. Cowart, *Tetrahedron Lett.*, 1986, **27**, 5563; (*c*) M. D. Cowart, I. Sucholeiki, R. R. Bukownik and C. S. Wilcox, *J. Am. Chem. Soc.*, 1988, **110**, 6204; (*d*) J. C. Adrian Jr and C. S. Wilcox, *J. Am. Chem. Soc.*, 1989, **111**, 8055; (*e*) D. R. Bond and J. L. Scott, *J. Chem. Soc., Perkin Trans. 2*, 1991, 47; (*f*) E. Yashima, M. Akashi and N. Miyauchi, *Chem. Lett.*, 1991, 1017.
5 (*a*) I. Sucholeiki, V. Lynch, L. Phan and C. S. Wilcox, *J. Org. Chem.*, 1988, **53**, 98; (*b*) T. H. Webb and C. S. Wilcox, *J. Org. Chem.*, 1990, **55**, 363.
6 P. Bouchet, C. Coquelet and J. Elguero, *J. Chem. Soc., Perkin Trans. 2*, 1974, 449.
7 M. L. Cerrada, J. Elguero, J. de la Fuente, C. Pardo and M. Ramos, *Synth. Commun.*, 1993, **23**, 1947.
8 E. Klingsberg, *J. Am. Chem. Soc.*, 1961, **83**, 2934.
9 R. M. Claramunt, J. Elguero and R. Garcerán, *Heterocycles*, 1985, **23**, 2895.
10 J. C. Adrian Jr. and C. S. Wilcox, *J. Am. Chem. Soc.*, 1992, **114**, 1398.
11 G. D. Mendenhall and P. A. S. Smith, *Org. Synth.*, 1966, **46**, 85.
12 R. K. Bartlett and I. R. Humphrey, *J. Chem. Soc. C*, 1967, 1664.

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† The previously unassigned ^1H and ^{13}C NMR spectra of parent Tröger's base **1** have been recorded and carefully assigned through two-dimensional and NOE experiments: ^1H NMR ($CDCl_3$) δ: 2.21 (s, 6H, Me), 4.10 (d, 2H, *J* 16.5 Hz, 6-H *endo*), 4.30 (s, 2H, 13-H), 4.64 (d, 2H, *J* 16.5 Hz, 6-H *exo*), 6.70 (d, 2H, *J* 1.5 Hz, 1-H), 6.94 (dd, 2H, *J* 8.1 and 1.5 Hz, 3-H), 7.03 (d, 2H, *J* 8.1 Hz, 4-H); ^{13}C NMR ($CDCl_3$) δ: 20.7 (Me), 58.5 (C-6), 66.9 (C-13), 124.6 (C-4), 127.1 (C-1), 127.3 (C-6a), 128.0 (C-3), 133.2 (C-2), 145.2 (C-4a).