1,2,5,6-Tetrazocines from Nitrile Imines and *tert*-Butyl Isocyanide

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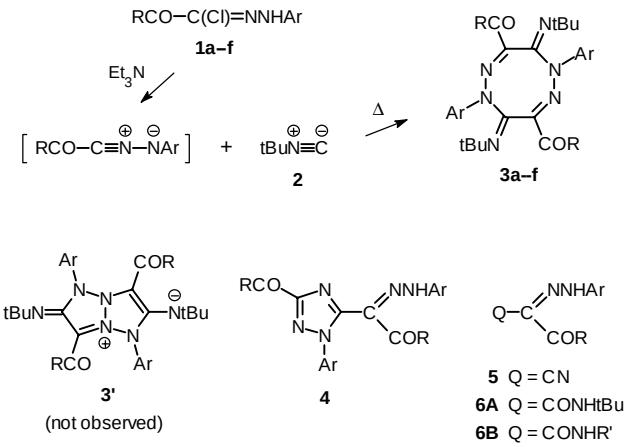
Abstract. *tert*-Butyl isocyanide (**2**) reacts with acceptor-substituted nitrile imines to give derivatives of tetrahydro-1,2,5,6-tetrazocines **3** along with substituted 5-hydrazonoyl-1,2,4-triazoles **4**. Replacement of **2** with aryl or *sec*-alkyl isocyanides leads to substituted α-hydrazonoamides (**6B**) rather than to analogues of **3**; removal of the acceptor group in **1** is likewise detrimental. – The structure of **3** has been established by means of an X-ray diffraction analysis of **3d**.

The reaction of nitrile imines with isocyanides – originally viewed as a route to four-membered rings [1] – proved in practice to be rather a source of 1,2,3- or 1,2,4-triazolium salts and pyrazoles [2]. On extending our experiments to C-acyl nitrile imines we encountered a further product that was unexpected: when the hydrazonoyl chlorides **1** were treated with *tert*-butyl isocyanide (**2**) and triethylamine in a manner similar to ref. [2b], deep yellow crystals could be separated whose EI mass spectra disclosed that **1** and **2** had reacted in a 2:2 molar ratio. Since the ^{1}H and ^{13}C NMR spectra exhibited only one RCO, Ar and *tert*-butyl group, a symmetrical structure such as **3** – formally a dimer of the linear 1:1 adduct of nitrile imine and **2** – was envisaged. Yet, bearing in mind that compounds claimed as 1,2,5,6-tetrazocines [3] were later shown to be (mesoionic, 10 π aromatic) 1,3a,4,6a-tetraazapentalenes [4], we also considered the isomeric structure **3'**. According to NMR, the methylene protons of the OEt ligand of the derivatives **b**,**d**,**f** are diastereotopic. This observation would be consistent with **3** in the case of slow ring inversion, but it would likewise account for **3'** in the case of restricted rotation of the CO_2Et group. Action of boiling hydrochloric acid on the derivative **c** [5] produced the nitrile **5c**, which again might point to either system. High resolution technique revealed that **5c** also occurred as a fragment in the mass spectrum of the above product [6], and **5a**,**b**,**d**–**f** were observed accordingly. We therefore performed an X-ray analysis of the derivative **d**, this eventually established structure **3** (see Fig. 1).

Although the molecule possesses no crystallographic symmetry, the central eight-membered ring displays twofold symmetry to a good approximation, as can be seen from the torsion angle sequence –99, 52, 20, 9, –98, 51, 20, 9° (starting



1, 3–6A	R	Ar	R'	6B
a	Me	Ph		
b	OEt	Ph		
c	Me	4-MeC_6H_4	4-MeC_6H_4	**a**
	Me	4-MeC_6H_4	*i*-Pr	**b**
d	OEt	4-MeC_6H_4		
e	Me	4-BrC_6H_4		
f	OEt	4-BrC_6H_4	c-C_6H_{11}	**c**

Scheme 1 Title reaction including structures of valence isomer **3'**, degradation product **5**, and side products **4** and **6**

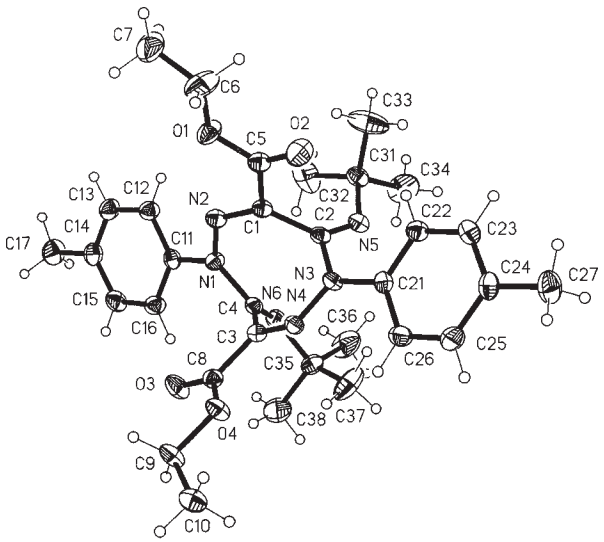


Fig. 1 Structure of compound **3d** in the crystal. Ellipsoids represent 50% probability levels. Hydrogen radii are arbitrary

  1436-9966/99/3410X-707 $ 17.50 + .50/0

about C1–C2 and moving clockwise in Fig. 1). The positions of the double bonds are unambiguously determined by the bond lengths C1–N2 and C3–N4 1.298(2), C2–N5 1.256(2), C4–N6 1.261(2) Å. Unusually wide sp^2 angles are observed as follows: C1–C2–N5 131.0(2), C3–C4–N6 130.8(2), C4–C3–N4 129.7(2), C2–C1–N2 129.1(2)°.

Variable temperature ^{1}H NMR spectra of **3d** were recorded in order to determine the activation barrier to inversion of the tetrazocine ring. From ambient temperature to the limiting temperature of +120 °C, the complex *AB*X$_3$ pattern of the OCH_2 protons gradually changed into a quartet with a small additional splitting. No signal broadening occurred at intermediate temperatures. The spectra could be simulated by assuming a static system with the chemical shift difference of the methylene protons decreasing as the temperature was raised. The simulation of dynamic spectra with increasing chemical exchange rates of the OCH_2 protons gave results that disagreed with the experimental findings. Hence, the effect observed was merely a chemical shift change with temperature. The chemical shift difference of ≤ 7 Hz at + 120 °C indicates that the free energy barrier to tetrazocine ring inversion in **3d** is larger than 88 kJ mol^{-1} at this temperature.

From all reaction mixtures we isolated as a second product a triazole of type **4**. This compound arises by dequaternization (loss of isobutene) of the less stable 4-*tert*-butyl-1,2,4-triazolium salt which is formed initially (*cf*. ref. [2b]). Its structure follows from comparison with the data of close congeners (**4**: Ar in place of RCO) [7a]. Owing to traces of moisture, minute amounts of the respective α-hydrazonoamides **6A** may also be separated (*e.g*. **6Ac** [7b]). Investigating the scope of the title reaction, we found that **2** cannot be replaced with aryl or *sec*-alkyl isocyanides, nor can RCO in **1** with an Ar ligand: experiments with phenyl, *p*-tolyl, isopropyl or cyclohexyl isocyanide gave the aforementioned amides, *e.g*. **6Ba**–**c** [8], and reactions of **2** with diaryl nitrile imines produced the aryl analogues of **4** (including their quaternary precursors) and 2,4-diaryl-2*H*-1,2,3-triazoles [9].

Apart from representing a novel nitrile imine reaction, the process **1/2** → **3** yields the first 1,2,5,6-tetrazocine derivative having cyclic unsaturation [10]; in addition, it provides the first example for constructing an eight-membered heterocycle from an isocyanide [11].

Experimental

M.p.: Kofler microscope. – IR: Philips PU-9800 FTIR. – UV/Vis: Philips PU-8730. – MS: Finnigan MAT 8400. – NMR: Bruker AM-400 (400.1 and 100.6 MHz for ^{1}H and ^{13}C, resp.); theoretical ^{1}H NMR spectra were generated using Bruker programs Win-DAISY 4.0 (static spectra) and Win-Dynamics 1.0 (dynamic spectra) . – Starting materials **1a**,**c**,**e** [12], **1b**,**d**,**f** [13], **2** [14] as well as phenyl, *p*-tolyl [15], isopropyl and cyclohexyl isocyanides [16] were made according to (or by adopting) literature procedures. – The new compounds **3a**–**f**, **4a**–**f**, **6Ac** and **6Ba**–**c** gave correct CHN microanalyses.

Reaction of the Hydrazonoyl Chlorides 1a–f with *tert*-Butyl Isocyanide (2) (General Procedure)

To a stirred solution of 5 mmol of the respective hydrazonoyl chloride **1** and 0.42 g (5 mmol) **2** in 25 ml anhydrous benzene were added 2.5 ml (ca. 18 mmol) triethylamine. The mixture was heated at reflux for 1 h, then cooled to room temperature and diluted with 25 ml petroleum ether. After standing for 2–

Table 1 Preparative, IR and MS data of **3a**–**f**, **4a**–**f**, **6Ac** and **6Ba**–**c**; UV/Vis data of **3a**,**b** and **4a**,**b**

Comp.	Yield (%)	*M.p.* [c] (°C)	recrystallized from	FTIR [e] ν (cm^{-1}) NH (**4, 6**); CO (**3,4,6**)	UV/Vis [g] λ_{max} (lg ε)	EIMS [h] *m/z* (%) M$^+$; **5**$^+$
3a	37	204–207	EtOH	1673	246 (4.12), 302 (4.13), 350 (4.36)	486 (13); 187 (100)
3b	23	179–181	MeOH	1702	245 (4.14), 314 (4.20), 344 (4.31)	546 (6); 217 (100)
3c	41	193–195	MeOH	1674		514 (19); 201 (100)
3d	27	195–197	MeOH	1699		574 (8); 231 (100)
3e	30	206–207	EtOH	1675		642/644/646 (6) [i]; 265/267 (54)
3f	37	182–185	EtOH	1696		702/704/706 (2) [i]; 295/297 (49)
4a	29	231–236	EtOH	3258; 1704, 1642	238 (4.21), 355 (4.24)	347 (100)
4b	55	130–135	petroleum ether [d]	3252; 1728, 1683	233 (4.30), 358 (4.32)	407 (100)
4c	35	183–187	petroleum ether	3276; 1704, 1674		375 (100)
4d [a]	57	131–138	petroleum ether	3212, 3169; 1738, 1672		435 (100)
4e	25	213–217	petroleum ether	3248; 1704, 1669		503/505/507 (92) [i]
4f	33	133–135	petroleum ether	3223; 1739, 1686		563/565/567 (100) [i]
6Ac [b]	8	97–101	EtOH	3322; 1700		275 (100)
6Ba	18	168–171	EtOH	1662 [f]		309 (100)
6Bb	7	100–102	EtOH	3251; 1656		261 (100)
6Bc	11	126–127	EtOH	3296; 1686		395/397 (100)

[a]) 1:1 Mixture of (*E*)- and (*Z*)-isomer [δ_H (NH): 11.45/12.78 ppm; *cf*. Table 2: **4b**]. [b]) 1:1 Mixture of (*E*)- and (*Z*)-isomer [δ_H (NH): 9.46/14.87 ppm]. [c]) **3a**–**f** with decomp. [d]) 40–70 °C. [e]) In KBr. [f]) NH not detectable. [g]) In EtOH. [h]) 70 eV; ion source temperature (°C): **3a**, 120; **3b**, 110; **3c**, 123; **3d**, 174; **3e**, 202; **3f**, 151; **4a**, 162; **4b**, 146; **4c**, 145; **4d**, 139; **4e**, 173; **4f**, 173; **6Ac**, 39; **6Ba**, 131; **6Bb**, 20; **6Bc**, 106. [i]) Rel. intensity with **3e**,**f** and **4e**,**f** refers to second peak.

Table 2 ^{1}H and ^{13}C NMR data of **3a**–**f**, **4b**,**c** and **6Ba**,**c**

Comp.	^{1}H NMR [a] δ (ppm); *J*, *N* (Hz)	^{13}C NMR [a] δ (ppm)
3a	1.22 (18H), 2.48 (6H), 7.18–7.21 (m, 2H), 7.36–7.40 (m, 4H), 7.40–7.71 (m, 4H)	25.9 (q), 29.7 [3C] (q), 57.4, 120.2 [2C] (d), 125.1 (d), 128.5 [2C] (d), 141.1, 142.9, 144.8, 196.4
3b	1.24 (t, *J* = 7, 6H), 1.27 (18H), 4.20–4.33 (m, 4H), 7.13–7.17 (m, 2H), 7.32–7.36 (m, 4H), 7.62–7.64 (m, 4H)	14.1 (q), 29.8 [3C] (q), 57.4, 62.1 (t), 119.8 [2C] (d), 124.8 (d), 128.5 [2C] (d), 134.5, 142.9, 143.6, 162.2
3c	1.21 (18H), 2.35 (6H), 2.46 (6H), 7.17/7.59 (AA'BB', *N* = 8, 8H)	20.8 (q), 25.9 (q), 29.7 [3C] (q), 57.3, 120.3 [2C] (d), 129.1 [2C] (d), 134.9, 140.7, 140.8, 145.1, 196.4
3d	1.25 (18H), 1.26 (ABX_3, 6H), 2.33 (6H), 4.19–4.34 (*AB*X$_3$: δ_A = 4.24, δ_B = 4.29, J_{AB} = –10.9, J_{AX} = 7.1, J_{BX} = 7.2, 4H) [b], 7.14 / 7.51 (AA'BB', *N* = 8.6, 8H)	14.1 (q), 20.8 (q), 29.8 [3C] (q), 57.2, 62.0 (t), 119.9 [2C] (d), 129.0 [2C] (d), 134.1, 134.4, 140.7, 143.8, 162.3
3e	1.20 (18H), 2.47 (6H), 7.48/7.56 (AA'BB', *N* = 9, 8H)	25.8 (q), 29.7 [3C] (q), 57.5, 118.3, 121.6 [2C] (d), 131.6 [2C] (d), 141.3, 141.8, 144.5, 196.3
3f	1.25 (18H), 1.26 (t, *J* = 7, 6H), 4.22–4.31 (m, 4H), 7.45/7.51 (AA'BB', *N* = 9, 8H)	14.1 (q), 29.8 [3C] (q), 57.5, 62.3 (t), 117.8, 121.2 [2C] (d), 131.5 [2C] (d), 134.7, 141.8, 143.3, 162.0
4b	1.03 (t, *J* = 7, 3H), 1.47 (t, *J* = 7, 3H), 4.04 (q, *J* = 7, 2H), 4.54 (q, *J* = 7, 2H), 7.05–7.54 (4m, 10H), 12.79 (1H) [c]	13.6 (q), 14.3 (q), 61.3 (t), 62.0 (t), 115.0 [2C] (d), 116.0, 124.2 [2C] (d), 124.3 (d), 129.0 (d), 129.3 [4C] (d), 137.9, 141.5, 151.2, 154.2, 159.8, 162.2
4c	2.32 (3H), 2.33 (3H), 2.40 (3H), 2.62 (3H), 7.12 (part of AA'BB', *N* = 8, 2H), 7.25–7.29 (overlapping AA'BB', 4H), 7.38 (part of AA'BB', *N* = 8, 2H), 11.45 (1H)	20.8 (q), 21.2 (q), 24.6 (q), 26.7 (q), 115.4 [2C] (d), 123.6 [2C] (d), 126.6, 129.8 [2C] (d), 129.9 [2C] (d), 133.7, 135.7, 139.6, 139.9, 146.8, 158.8, 190.5, 193.8
6Ba	2.32 (3H), 2.34 (3H), 2.54 (3H), 7.14/7.27 (AA'BB', *N* = 8, 4H), 7.17/7.49 (AA'BB', *N* = 8, 4H), 11.38 (1H), 14.73 (1H)	20.88 (q), 20.91 (q), 26.0 (q), 115.7 [2C] (d), 120.8 [2C] (d), 125.6, 129.5 [2C] (d), 130.1 [2C] (d), 134.3, 134.6, 135.2, 139.4, 163.0, 199.2
6Bc	1.2–2.0 (m, 10H), 1.40 (t, *J* = 7, 3H), 3.80–3.89 (m, 1H), 4.31 (q, *J* = 7, 2H), 7.21/7.45 (AA'BB', *N* = 9, 4H), 8.99 (d, *J* = 8, 1H), 14.63 (1H)	14.2 (q), 24.6 (t), 25.5 [2C] (t), 32.6 [2C] (t), 47.5 (d), 61.3 (t), 116.9, 117.0 [2C] (d), 118.5, 132.3 [2C] (d), 141.3, 163.8, 166.2

[a]) In $CDCl_3$; unspecified signals are singlets. [b]) Analyzed by iteration. [c]) Negligible singlet at δ 11.56.

3 h the triethylammonium chloride was filtered off and the filtrate concentrated *in vacuo*. The residue was dissolved in 5 ml ethanol and kept overnight at 0 °C to allow yellow crystals of the *substituted tetrahydro-1,2,5,6-tetrazocine* **3** to separate which were collected by filtration and washed with a small amount of cold ethanol. For data, see Table 1 and 2. – The mother liquor of **3** was concentrated and the residue dissolved in petroleum ether; on standing at 0–5 °C the *substituted 1,2,4-triazole* **4** crystallized (for data, see Table 1 and 2). The filtrate of **4** was chromatographed on silical gel (dichloromethane as eluent) to yield successively: a second crop of **3**, traces of the *substituted 2-hydrazonoamide* **6A** (for data of **6Ac**, see Table 1) and some more triazole **4**.

In the same fashion we treated: **1b** with phenyl and cyclohexyl isocyanides, **1c** with *p*-tolyl isocyanide, isopropyl and cyclohexyl isocyanides, and **1f** with cyclohexyl isocyanide. Work-up by column chromatography as detailed above afforded the *substituted 2-hydrazonoamides* **6Ba**–**c** (for data, see Table 1 and 2) and traces of *diethyl 4,8-bis(cyclohexylimino)-1,5-di-(p-tolyl)-1,4,5,8-tetrahydro-1,2,5,6-tetrazocine-3,7-dicarboxylate* (cyclohexyl analogue of **3d**) which could not be obtained analytically pure [MS (70 eV, 154 °C), *m/z* (%): 626 (M^+, 3). – ^{1}H NMR ($CDCl_3$): δ/ppm = 1.1–1.8 (m, 20H), 1.31 (t, *J* = 7 Hz, 6H), 2.34 (s, 6H), 3.29 (m_c, 2H), 4.26/4.36 (2dq, J_{AB} = 11 Hz, $J_{AX,BX}$ = 7 Hz, 4H), 7.15/7.45 (AA'BB', *N* = 8 Hz, 8H)].

Reaction of the 1,2,5,6-Tetrazocine 3d with Hydrochloric Acid

A mixture of 0.51 g (1mmol) **3d** and 10 ml 6N HCl was heated at reflux for 30 min. The cooled solution was neutralized with Na_2CO_3 and extracted with dichloromethane (3 × 20 ml) to give, after chromatography on silica gel (dichloromethane as eluent), 0.26 g (65%) *3-oxo-2-[(p-tolyl)hydrazono]butyronitrile* (**5c**) which was recrystallized from ethyl acetate, *m.p.* 172–174 °C (ref. [17] 171–174 °C); FTIR (KBr): ν/cm^{-1} = 3227, 2207, 1657; the ^{1}H and ^{13}C NMR data were consistent with the literature [17].

X-Ray Structure Determination of 3d

Data were measured using Mo-K_α radiation on a Bruker SMART 1000 CCD diffractometer. The structure was solved by direct methods and refined anisotropically on F^2 using all reflections (program SHELXL-97 [18]). Hydrogen atoms were included using a riding model or as rigid methyl groups. *Crystal data*: $C_{32}H_{42}N_6O_4$, *M* = 574.72, crystal size 0.25 × 0.20 × 0.18 mm, monoclinic, $P2_1/n$, *a* = 10.3570(10), *b* = 24.556(3), *c* = 12.8721(14) Å, β = 107.101(3)°, *U* = 3129 Å^3, *Z* = 4, μ (Mo K_α) = 0.08 mm^{-1}, D_x = 1.220 Mg m^{-3}, *T* = –130 °C. Reflections: total 21845 to 2θ 55°, unique 7177 (R_{int} 0.070). Final *wR*2 0.113, *R*1 0.046; 389 parameters; *S* 0.92, max. $\Delta\rho$ 0.29 e Å^{-3}.

Full details (excluding structure factors) have been deposited at the Cambridge Crystallographic Data Centre under the reference number CCDC 143891. Copies may be obtained free of charge from the Director, CCDC, 12 Union Rd., GB-Cambridge CB2 1EZ (Telefax: Int.+ 1223/336033; E-mail: deposit@ccdc.cam.ac.uk).

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[5] The material proved resistent not only to 6N–14N NaOH but also to oxidants such as potassium permanganate.

[6] A peak appearing at *m/z* = 201.0899 can be assigned to **5c** (exact mass calculated for $C_{11}H_{11}N_3O$ 201.0902); 4-acetyl-1-(*p*-tolyl)-1*H*-1,2,3-triazole has the same composition, but this species can be ruled out because of absence of *m/z* = 173 (loss of molecular nitrogen).

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