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CHEMISTRY OF AMIDRAZONES—III
ADDITION–CYCLISATION OF AMIDRAZONES WITH CARBODI-IMIDES

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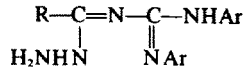
Abstract—Amidrazones react with diarylcarbodi-imides in dimethylformamide at *ca.* 100° to yield 3-substituted 5-arylamino-1,2,4-triazoles and their 4-aryl-analogues. The triazoles arise directly from the presumed intermediate linear mono-adducts by loss of arylamine or ammonia. The factors governing the direction of cyclisation are discussed.

The use of amidrazone derivatives in heterocyclic synthesis[1] was recently extended by the cyclisation of novel thioacylated amidrazones to 1,3,4-thiadiazoles.[2] We now report a group of comparable reactions, based on the production and ring-closure of adducts of amidrazones with heterocumulenes. The reactions, which provide a useful route to 1,3,4-thiadiazoles and 1,2,4-triazoles, were studied in their simplest form using unsubstituted amidrazones **1** that have recently become more readily available.[3] This paper deals with their interaction with carbodi-imides.

Amongst heterocumulenes,[4] carbodi-imides[5] **2** are remarkable for the variety of their addition reactions, and for the wide range of heterocyclic products that are accessible by ring-closure of the resulting adducts. Of the numerous examples studied,[5] addition-cyclisations of carbodi-imides with (thio)semicarbazides,[6] amino-[6] and diamino-guanidines,[7] diguanides[8] and (thio)carbonohydrazides[9] are particularly relevant to the present work.

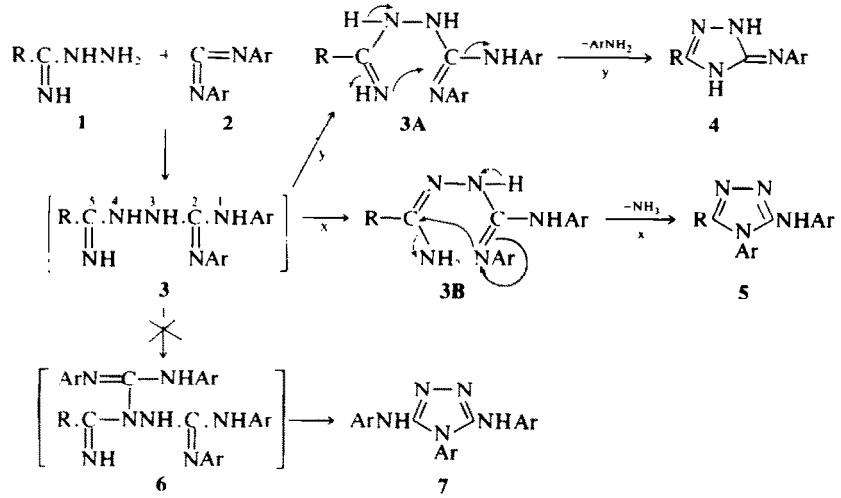
The interaction of amidrazone salts **1** and carbodi-imides **2** in dimethylformamide at 80–90° produced good yields of substituted 1,2,4-triazoles **4**, **5** directly in one step. The structure of the heterocyclic products was established by a comparison of selected examples with authentic material. In agreement with precedent,[5–8] the reaction is thought to involve the initial addition of the heterocumulene at the ultimate hydrazino-nitrogen of the amidrazone, immediate loss of ammonia or arylamine from the resulting linear adducts **3** affording the observed products. Attempts to isolate the presumed intermediates **3** were not successful; under mild conditions, carbodi-imide was largely recovered, and the heterocyclic compounds **4** and **5** were obtained in low yield. Addition of the carbodi-imide at the alternative positions (in **1**, giving **3C** or **3D**) may be discounted; although **3C** is also convertible into **4** by loss of arylamine, it cannot, even in the unlikely event of its hydrazino-group being cleaved, form the observed product **5** by elimination of ammonia; **3D** cannot be cyclised to triazoles at all.



3C

3D

With acetamidrazone (**1**; R = Me), reaction proceeded almost exclusively with loss of ammonia (path x) to afford the 4-substituted 1,2,4-triazoles (**5**; R = Me; Ar = Ph, p-Tol). The alternative cyclisation (to **4**) occurred only to a

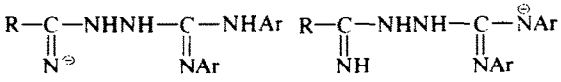


1a: R = Ph; **1b**: R = Me
4a: R = Ph, Ar = Ph
4b: R = Ph, Ar = pTol
2a: Ar = Ph; **2b**: Ar = pTol
5a: R = Ph, Ar = Ph
5b: R = Ph, Ar = pTol
5c: R = Me, Ar = Ph
5d: R = Me, Ar = pTol

minor extent; this was indicated, in one example, by the isolation of small quantities (8%) of *s*-triphenylguanidine, arising by the addition of unreacted diphenylcarbodi-imide to the liberated aniline. In contrast, loss of arylamine (path y) and formation of **4** (R = Ph; Ar = Ph, p-Tol; 60 and 45%, respectively) was the predominant reaction when benzamidrazone was employed. Phenylacetamidrazone gave inseparable mixtures.

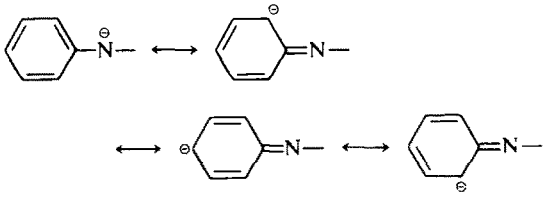
The ring-closure is visualised to involve the usual intramolecular nucleophilic attack, in the primary intermediate (**3**), of an imino-nitrogen on the (remote) carbon atom. The prevailing direction of cyclisation (path x or y) will depend on the relative nucleophilicity of the imino- or arylimino-groups, the relative electrophilic power of the carbon atoms C-2 or C-5, and on steric factors. The only significant structural variations, to which the preferred course of the reaction should ultimately be traced, are changes in the substituent R (Alk or Ar in **3**). Since, however, the powerful bases acetamidine and benzamidine (pK_a 12.4[10] and 11.2[11] respectively) do not differ materially, as do aliphatic and aromatic amines,[12] in their basic strength, differences in the overall electronic effects of alkyl and aryl groups in this structural environment are not likely to be large. The nucleophilicity of the imino-group in amidines (and hence in **3**), and the location of the most nucleophilic centre in **3**, should therefore be reasonably independent of the nature of these groups.

The observed direction of cyclisation (path x or y) may thus be rationalised in the following terms: in the linear intermediate (**3**), carbon atoms C-5 and C-2 are flanked by two or three nitrogen atoms of basic groups, respectively. Carbon atom C-5, being exposed to a smaller electron-releasing effect of its surroundings than C-2, is the centre of relatively lower electron density. The consequent preferred nucleophilic attack at C-5 favours pathway x, and the superior leaving properties of an amino- over an anilino-group may reinforce this tendency. Reaction should therefore occur predominantly with loss of ammonia (path x), as is indeed observed in examples employing acetamidrazone. The occurrence of the alternative cyclisation (path y) as parallel or main reaction in examples involving benzamidrazone may be ascribed to steric hindrance, inhibiting the approach (in **3**) of the bulky arylamino-group to carbon atom C-2.



3E **3F**

An interpretation of the ring closure by a mechanism involving preliminary anion-formation[2] leads to the same conclusion. Although the reaction occurs in the absence of base (contrast Part IV, following paper), the proton-accepting properties of dimethylformamide[13] would seem to make the formation of ionic species feasible. Each constituent portion of structure **3** being of pronounced basic character, the formation of **3F** (in preference to **3E**) as the most stable anion is justified on the basis of its stabilisation by delocalisation of its negative charge over the carbanion resonance hybrid:



The arylamino-group (in **3**) is therefore the predominating nucleophilic centre, and cyclisation along path x is favoured.

Although the interaction of carbodi-imides with imidoylhydrazino- (**8a–d**)[6,7] or related compounds[8,9,14] results in diverse reactions, a unified scheme emerges from the accumulated information.[6–9] The heterocumulene is added at the hydrazino-group (**8** → **9** → **10**), unless this be blocked by substitution, especially by hydrazone formation, when addition is diverted to the imino-group (**8** → **11** → **12**).[6,7] In some cases, the mono-adducts are sufficiently stable to be isolated (e.g. **9a–c**,[6] **12c**, **f**,[6] **g**[7]), but others (**9d**, **e**) cyclise spontaneously[6,7] to 1,2,4-triazoles; alkaline conditions promote this process almost invariably. The penultimate nitrogen of the hydrazino-group (in **9**) may compete strongly for the available carbodi-imide, even if present in only equimolar amounts, resulting in the formation of di-adducts of type **10**.[6,7,14] Although these are not isolable themselves, the nature of certain of the triazoles obtained (e.g. **7**) leaves no doubt of their role as intermediates; their close structural analogues (**10A**)[14] derived from ethoxycarbonylhydrazine are in fact stable crystalline solids.

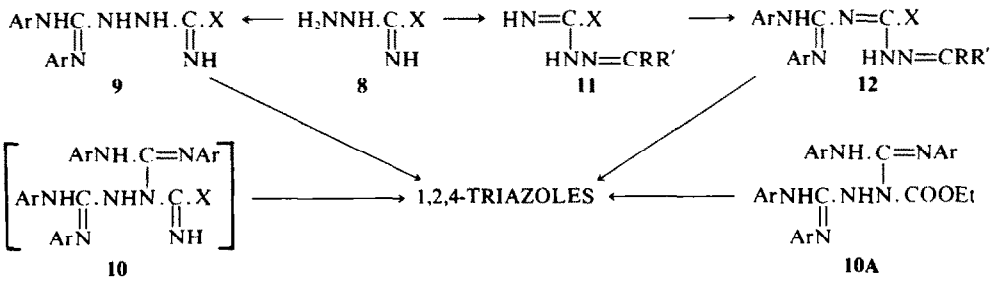
In the present reaction, the primary mono-adducts (**3**) are clearly cyclised so rapidly as to be not isolable. They are thus also unavailable for di-addition (to **6**), so that 3,4,5-trisubstituted 1,2,4-triazoles (**7**), one of the usual final products of addition-cyclisations of this type (e.g. from **9a–e**) are not formed.

EXPERIMENTAL

General. M.ps are uncorrected. The IR spectra were measured on a Unicam SP 200 instrument, using KBr discs.

3-Anilino-5-methyl-4-phenyl-1,2,4-triazole **5c**

A stirred solution of acetamidrazone HCl (1.32 g, 0.012 mole) in dimethylformamide (40 ml) at 80–90° was treated with



X: (a) SH, (b) OH, (c) NH_2, (d) $NHNH_2$,
(e) NHNHC(:NAr)NHAr, (f) SAlk, (g) NHN=CRR'

diphenylcarbodi-imide (1.94 g, 0.01 mole). The liquid was kept at this temperature for 30 min, then added to ice-water. The precipitate (filtrate: F) gave opaque microprisms (1.60 g, 60%) of **5c**, m.p. 240–242° (from EtOH; 40 ml per g, recovery 75%). Lit. m.p. 228–230°,[6] 227–228°[15] (Found: C, 72.2; H, 5.2; N, 21.8. Calc. for $C_{15}H_{14}N_4$: C, 72.0; H, 5.6; N, 22.4%). IR: 3400ms, 3230, 3180m (doublet), 3070m (NH); 2920m (CH_3); 1600s (C=N); 1550s br (C–N–H); 1500s, 755s br, 690s (Ph); 1395m, 1230m, 1010m cm^{-1}. Filtrate F was made just acid with HCl; the resulting white precipitate, collected after 12 h at 0°, was *s*-triphenylguanidine (0.23 g, 8%), m.p. 142–144° (Lit.[16] m.p. 144°) (from 50% EtOH). (Found: C, 78.8; H, 5.9; N, 15.2. Calc. for $C_{19}H_{17}N_3$: C, 79.4; H, 5.9; N, 14.6%), further identified by its IR spectrum.

3-Methyl-5-p-toluidino-4-p-tolyl-1,2,4-triazole **5d**

The use, in the foregoing procedure, of di-p-tolylcarbodi-imide (2.22 g, 0.01 mole) in dimethylformamide (10 ml) gave a turbid liquid, which was stirred at 100° for 1 h, added to H_2O (250 ml), the suspension stirred to effect coagulation, and the product (m.p. 220–225°; 1.82 g, 65%) collected after storage at 0°. It gave prismatic needles of **5d**, m.p. 224–226° (from EtOH) (Found: C, 73.4; H, 6.5; N, 20.4. $C_{17}H_{18}N_4$ requires: C, 73.4; H, 6.5; N, 20.1%). IR: 3230, 3180m (doublet), 3000m (doublet) (NH); 2900m (CH_3); 1615, 1600m (doublet) (C=N); 1555s (C–N–H); 825s (1,4-disub. aryl); 1520s, 1255m, 1015m cm^{-1}.

In a lower temp range (*ca.* 50° for 45 min), the yield of this 1,2,4-triazole was reduced (15%), much of the carbodi-imide being recovered (50%).

3-Anilino-4,5-diphenyl-1,2,4-triazole **5a** *and 3-anilino-5-phenyl-1,2,4-triazole* **4a**

A stirred solution of benzamidrazone hydriodide[3] (2.63 g, 0.01 mole) in dimethylformamide (25 ml), treated dropwise at 90° with diphenylcarbodi-imide (1.94 g, 0.01 mole), was kept at this temp. during 30 min, then added to ice-water (200 ml). The fine precipitate coagulated slowly on stirring; it was collected, air-dried (1.75 g), and dissolved in boiling EtOH (150 ml). The first crop (m.p. 210–214°, 0.25–0.37 g, 8–12%) (filtrate F) was **5a**, forming felted needles, m.p. 209–211° (from EtOH, 500 ml per g, recovery 60%) (Found: C, 76.4; H, 5.0; N, 18.4. $C_{20}H_{16}N_4$ requires: C, 76.9; H, 5.1; N, 17.95%). IR: 3360m, 3050m (NH); 1665s (C=N); 755s, 690s (Ph); 1600s, 1525s, 1450s, 1375m, 1130m, 970m, 730s cm^{-1}. Filtrate F gave, on successive evaporation to small bulk, needles (1.3–1.5 g, 56–64%) of **4a**, m.p. 240–242° (from EtOH). Lit.[17] m.p. 242° (Found: C, 71.2; H, 5.1; N, 23.6. Calc. for $C_{14}H_{12}N_4$: C, 71.2; H, 5.1; N, 23.7%). IR: 3330m, 3060m, 2920m (NH); 1605ms (C=N); 1555s br (C–N–H); 740s, 695s (Ph); 1530s, 1410m, 1245m, 1130m, 990m cm^{-1}.

3-Phenyl-5-p-toluidino-1,2,4-triazole **4b**

A solution of benzamidrazone hydriodide[3] (1.32 g, 0.005 mole) and di-p-tolylcarbodi-imide (1.11 g, 0.005 mole) in dimethylformamide (18 ml) was boiled under reflux for 1 h, then cooled and stirred into H_2O (120 ml). The precipitate (*ca.* 1.1 g) gave, on crystallisation from EtOH (20 ml), opaque minute felted needles (0.31–0.38 g, 25–30%) of **4b**, m.p. 242–244°. Lit.[17] m.p. 244° (Found: C, 73.0; H, 5.6; N, 22.55. Calc. for $C_{15}H_{14}N_4$: C, 72.0; H, 5.6; N, 22.4%). IR: 3300ms, 2900m (NH); 1620, 1605m (doublet) (C=N); 1550s (C–N–H); 825m (1,4-disub. aryl); 730ms, 695s (Ph); 1530ms, 1410m, 1245m, 1125m, 985ms cm^{-1}.

The combined later crops gave, after crystallisation from very little EtOH, prismatic needles (m.p. 182–185°; 0.22–0.37 g, 15–25%), consisting according to TLC and their composition, of a 1:1 addition compound of **4b** and its 4-p-tolyl-derivative **5b** (Found: C, 75.1; H, 5.8; N, 19.1. $C_{15}H_{14}N_4 . C_{22}H_{20}N_4$ requires: C, 75.25; H, 5.8; N, 19.0%). The latter triazole was not isolated pure; the crystals of the adduct turned grey on exposure to light, a property shown by analogous 3,4,5-trisubstituted 1,2,4-triazoles.[6] Already after 5 min boiling of the reaction mixture, **4b** was isolated in 25% yield, but little reaction occurred when the reaction mixture was stirred at 75–45° for 1 h (di-p-tolylcarbodi-imide being recovered, 90%).

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