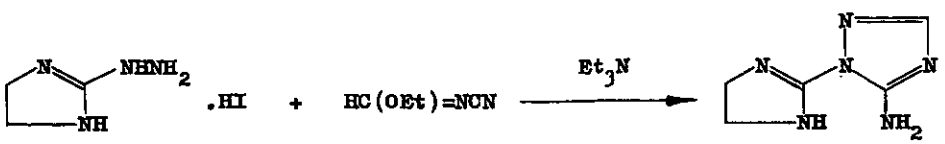
NEW CONDENSED TRI- AND TETRACYCLIC 1,2,4-TRIAZOLE RING SYSTEMS

Jan Světlík
Drug Research Institute, Palárikova 31, 811 04 Bratislava, Czechoslovakia

Abstract - A facile two step synthesis of 7,8-dihydroimidazo[1,2-e]-1,2,4-triazolo[1,5-a]-1,3,5-triazine and 1,2,4-triazolo[1',5':1,2]-1,3,5-triazino[5,6-a]benzimidazole is described. Heterocyclic hydrazines react easily with ethyl N-cyanoformimidate to form 1,2,4-triazole derivatives, which are then cyclized with ortho esters into hitherto unknown polyazaheterocycles.

The valuable pharmacological properties of condensed 1,2,4-triazoles are well documented[1]. In view of the current interest in the biological activity of these derivatives we wish to report here our research in the fused polycyclic system area.

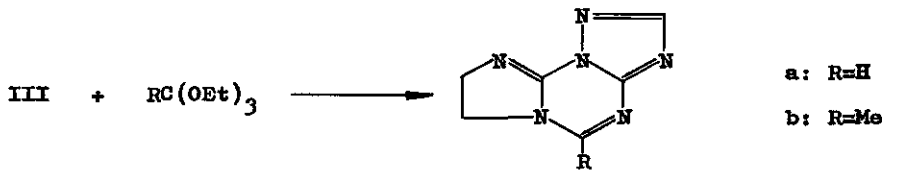
Readily accessible 2-hydrazino-4,5-dihydroimidazole hydriodide[2] (I) was a convenient starting compound in the synthetic pathway. In order to construct a functionalized triazole part of the target molecule the above compound was first converted into 5-amino-1-(4,5-dihydroimidazol-2-yl)-1H-1,2,4-triazole (III). This key precursor can be easily prepared on a large scale by cyclo-condensation of I with ethyl N-cyanoformimidate (II) following a modification of the Heckendorn and Winkler process[3] (Scheme 1). The reaction was carried out at temperature below 60 °C by slow and gradual addition of II to a stirred ethanolic solution of I and equimolar amount of triethylamine. The white precipitate, thoroughly washed with ether, was suitable for further handling[4].



I II III

Scheme 1

The next step in the synthetic route involves final linking of the preformed triazole unit onto the imidazoline ring. The reaction of the intermediate III with triethyl orthoformate was found to proceed under severe conditions. Thus, refluxing a mixture of III and approximately two molar equivalents of $HC(OEt)_3$ in dimethylformamide for 10 h afforded the parent heterocycle (IVa, Scheme 2) as a single product (50%). Attempts to convert III into IV in other media were unsuccessful despite the use of various types of solvents. However, the ring closure reaction can also be effected by treating III with $HC(OEt)_3$ in the presence of a catalytical amount of concentrated sulfuric acid. The desired product was formed over a 15 min period heating in an improved yield. The resulting crude crystalline solid was collected and recrystallized from ethanol to give IVa as colorless needles, m.p. 246-248 °C (59%). 7,8-Dihydroimidazo-[1,2-e]-1,2,4-triazolo[1,5-a]-1,3,5-triazine obtained here represents a new class of tricyclic bridgehead heterocycles. Finally, a fusion of III with triethyl orthoacetate provided the 5-methyl homologue (IVb, 47%) melting at 277-279 °C.

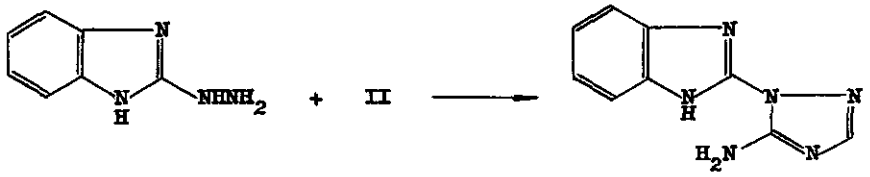


IVa-b

Scheme 2

The structures of IVa-b were established by elemental analyses and spectral measurements. The IR spectra[5] exhibited a strong peak near 1710 cm^{-1} attributable to the imidazoline C=N group absorbing at higher wave-number than usual due to strain from ring fusion. Apart from the intense band, uniformly observed at 1588 cm^{-1} indicating triazole ring stretching vibrations, a third strong band in the range 1548-1573 cm^{-1} may be ascribed to the triazine C=N absorption. In the ^{1}H-NMR spectra heteroaromatic protons of the basic skeleton IVa appeared as two singlets at 8.32 (triazine ring-proton, H-5) and 8.26 ppm (triazole ring-proton, H-2) as confirmed by heteronuclear tickling experiment[6]. Moreover, in the aliphatic region (3.87-4.38 ppm, CH_2-CH_2) AA'BB' splitting pattern was observed. The substituted tricyclic compound IVb revealed the following chemical shifts: 8.23 (H-2), 3.85-4.34 (CH_2-CH_2) and 2.36 ppm (CH_3).

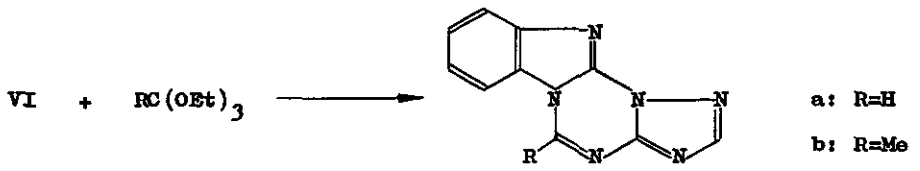
Because of the convenience and experimental simplicity of this reaction sequence it was decided to explore its possibilities for the preparation of benzo analogues of IVa-b via the above mentioned route. The required material, 2-hydrazinobenzimidazole (V), was synthesized according to the patent literature[7]. As expected, reaction of V with II proceeded rapidly to give 2-(5-amino-1H-1,2,4-triazol-1-yl)benzimidazole (VI, Scheme 3) in good yield.



V VI

Scheme 3

Without further purification VI[3] was cyclized with triethyl orthoformate. This was accomplished by heating in dimethylformamide at reflux temperature for 2 h. After evaporation of the solvent and recrystallization of the product from dimethylformamide 1,2,4-triazolo[1',5':1,2]-1,3,5-triazino[5,6-a]benzimidazole (VIIa, Scheme 4) was obtained in 65% yield, m.p. > 360 °C. A similar reaction of VI with triethyl orthoacetate led to its 5-methyl derivative VIIb, m.p. 286-288 °C (DMF), under reflux for only 1 h in 21% yield. The other cyclization mode using H_2SO_4 as a catalyst failed owing to the insolubility of the intermediate VI in the ortho ester.



VIIa-b

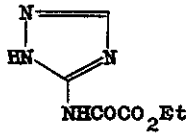
Scheme 4

In contrast to IVa-b the wave-number of the ring junction C=N band of VIIa-b decreased to 1650 cm^{-1} as a result of the conjugation in benzimidazole nucleus. The most striking feature in the ^{1}H-NMR spectrum of VIIa is the low-field resonance (9.92 ppm) of the proton in the 5 position, while H-2 (8.67 ppm) occurs as expected for those in the 1,2,4-triazole ring. The remaining signals consist of three multiplets for aromatic protons at 8.38 (H-10), 7.94 (H-7)

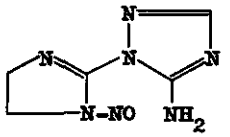
and 7.61 ppm (H-8 + H-9). Similar signals were observed for compound VIIb: 8.62 (H-2, s), 8.20 (H-10, dm, J=7.1 Hz), 7.90 (H-7, dm, J=7.4 Hz), 7.20 (H-8 + H-9, m) and 3.33 ppm (CH_3, s)[8].

Attempts with other cyclizing agents as BrCN, CS_2 or 1,1'-carbonyldiimidazole were unsuccessful. Unexpectedly, treatment of III with large excess of diethyl oxalate at reflux temperature for 4.5 h afforded the product VIII, indicating a scission of the single C-N bond joining the two ring systems[9].

Another approach was designed to provide an entry to a series of novel fused heterocycles incorporating 1,2,3,5-tetrazine skeleton, i.e. 5-aza analogues of IVa and VIIa, respectively. We intended to realize this by diazotization of the corresponding amino-substituted 1,2,4-triazoles (III and VI) and subsequent coupling with NH-C=N moiety of imidazoline or benzimidazole nucleus. Nevertheless, the desired products were not obtained. Instead, N-nitrosation took place in case of III yielding compound IX[10]. Derivative VI was found to be insoluble in both acetic acid and diluted mineral acids and therefore it did not react under the diazotization conditions.



VIII



IX

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2. M. Brugger and F. Korte, Justus Liebigs Ann. Chem., 1972, 764, 112.
3. R. Heckendorn and T. Winkler, Helv. Chim. Acta, 1980, 63, 1.

4. Yields of isolated crude intermediates: III (81%, m.p. 213-214 °C from ethanol), and VI (72%, m.p. 313-315 °C from ethanol).
   All new compounds gave satisfactory analytical (combustion and high resolution MS) and spectral (IR, NMR, MS) data.
5. IR spectra were measured in KBr disk on a Digilab FTS-14 spectrophotometer.
6. This will be published elsewhere together with ^{13}C-NMR analysis. ^{1}H-NMR spectra were recorded with a Jeol FX-100 spectrometer, solvent DMSO-d_6, 23 °C, TMS as an internal reference.
7. D. J. Fry and B. R. D. Whitear, British Patent, 813,866 (1959) [Chem. Abstr., 1960, 54, 121].
8. Varian XL-200 spectrometer, solvent DMSO-d_6. VIIa was measured at 80 °C, VIIb at 23 °C. The central signal of DMSO-d_5 (2.50 ppm) was used as a reference.
9. Identical in all respects with an authentic sample prepared according to the procedure of A. Kreutzberger and B. Meyer, Chem. Ber., 1972, 105, 3974.
10. Quantitative yield was obtained in acetic acid at room temperature, m.p. 165 °C (dec).

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