Heterocycles. CLVII. Oxidative Transformations of Some Heterocyclic Hydrazones with Lead Tetraacetate

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Reactions of hydrazones of heterocyclic aldehydes with lead tetraacetate in the presence or absence of dienophiles are described. We have found that during the reaction with lead tetraacetate the formed intermediate nitrilimines react preferentially with the acetate ion and not with the acetylenic dienophile. An exception is acrylonitrile which formed the cycloadduct. If the structure of the intermediate nitrilimine is such that a dipolar cycloaddition, involving the pyridine ring nitrogen, is possible, triazolopyridines are formed.

Oxidations of a wide range of hydrazones have been studied and the corresponding transformations have been reviewed[1-3]. Two different pathways are involved in these reactions, depending on the structure of the substrate. In general, aldehyde hydrazones, when oxidized with lead tetraacetate in acetic acid solution, give N-acyl-N'-acetylhydrazines (**1 → 2**) and the reaction is postulated to involve nitrilimines as intermediates. On the other hand, ketone hydrazones are transformed into azoacetates (**3 → 4**). Although the transformations of hydrazones of aliphatic or aromatic aldehydes have been investigated, there are almost no reports concerning heterocyclic aldehyde hydrazones. There is, however, a report on pyridyl-2-aldehyde phenylhydrazone which was oxidized with lead tetraacetate in dichloromethane into the corresponding N-acetyl-N'-(2-picolinoyl)-phenylhydrazine (**10**)[4]. On the other hand, compounds with the reverse functionality, *i. e.* aldehyde hydrazones of hydrazinoheterocycles, react in a different manner.

We have shown that the dehydrogenative cyclizations of alkylidene or arylidene derivatives of 3-hydrazinopyridazines with either bromine or lead tetraacetate afford the corresponding s-triazolo(4,3-b)pyridazines under mild reaction conditions[5-9]. This procedure has been employed also for the preparations of other s-triazoloazines[10-17] or s-triazoloazoles[18-22]. Apparently, the fusion of a triazole ring to a five-membered ring is not so easy as the fusion to a six-membered heterocycle, since a competing process, *i. e.* acetoxylation of the hydrazone has been observed[23,24].

Although several mechanistic pathways have been considered for the reactions of hydrazones with lead tetraacetate, a polar mechanism has been strongly suggested by the kinetic measurements data[24,25]. Moreover, evidence has been obtained of intermediate nitrilimines (**5**) which have been trapped with dienophiles[26-28].

In view of these findings, it appeared of interest to investigate oxidative transformations of heterocyclic aldehyde hydrazones and to employ such model compounds which would allow also the possible participation of a ring nitrogen in these transformations. One can anticipate that the intermediate nitrilimines (5) may be either trapped in the presence of an appropriate dienophile in a 1,3-dipolar cycloaddition reaction or that a concurrent cyclization of the nitrilimine as a 1,5-dipolar species (5c) into 6 should take place (scheme I). Alternatively, an attack of acetic acid would give the acetoxy azo-compound (7) which could rearrange into the corresponding N-acetyl-N'-acylhydrazine derivative (8).

Pyridyl-2-aldehyde phenylhydrazone (9), when treated with lead tetraacetate in the presence of dimethyl acetylenedicarboxylate afforded only the corresponding N-acetyl-N'-picolylhydrazine (10). This indicates that the intermediate nitrilimine is attacked preferentially by the acetate ion rather than to

Scheme I
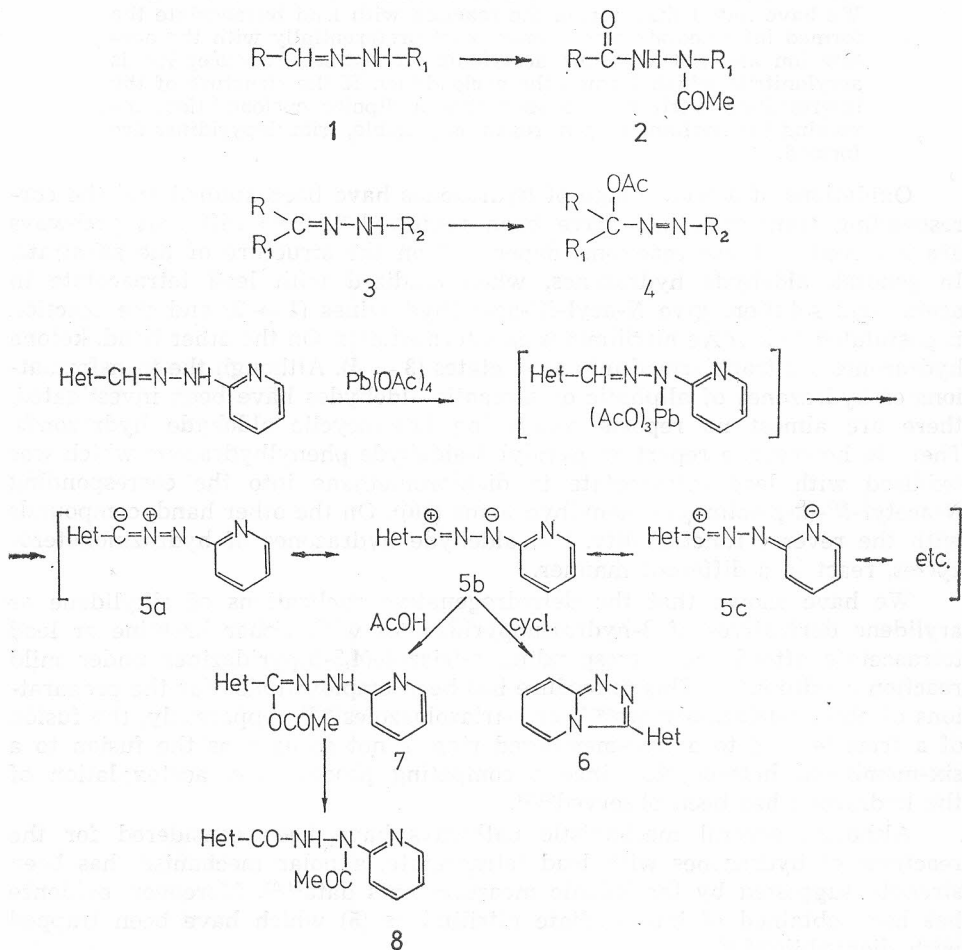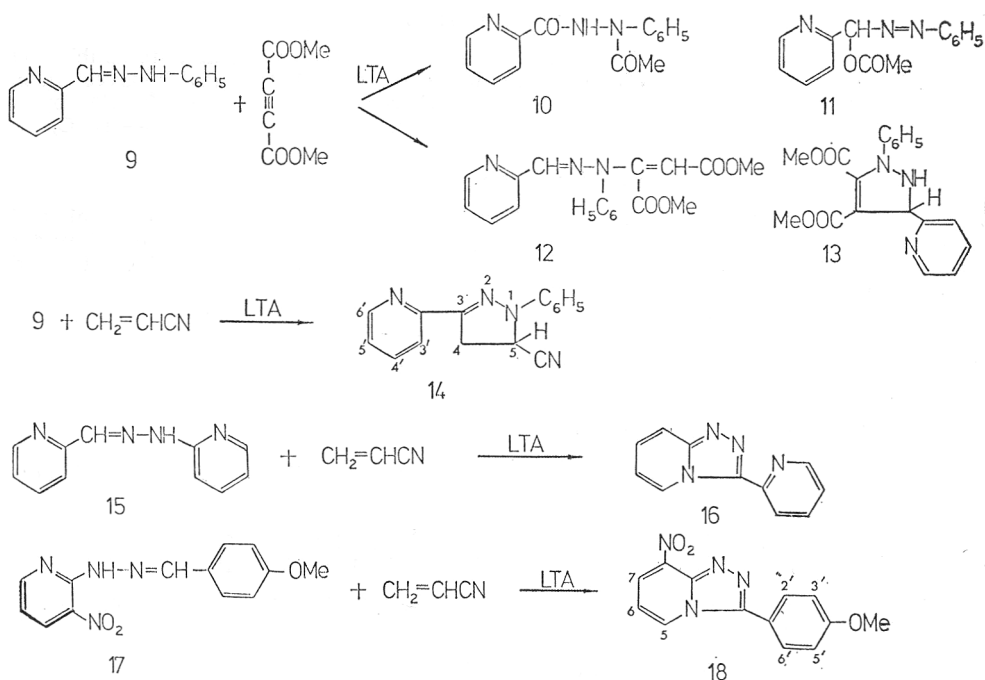
undergo a 1,3-dipolar cycloaddition reaction with the acetylenic dienophile. For the product obtained an alternative structure of an acetoxy compound (11) is theoretically possible. This compound was not isolated, probably owing to its easy rearrangement to (10) which was found to be identical with an authentic specimen. If the same reaction was conducted in the absence of lead tetraacetate the adduct (12) was isolated in moderate yield. An alternative structure for this compound, i. e. cycloaddition product (13) is ruled out by the NMR data since two singlets, corresponding to two different —CH= groups could be observed.

If acrylonitrile was used as dienophile, the intermediate nitrilimine, generated by lead tetraacetate oxidation of pyridyl-2-aldehyde phenylhydrazone, could be trapped and the cycloaddition product (14) was obtained. Its structure is consistent with the analytical and NMR spectroscopic data. Moreover, the mass spectrum of 14 showed a fragmentation pattern consistent with the above observations. The major fragmentation observed involves the loss of HCN $(M^+ - 27)$, acrylonitrile $(M^+ - 53)$ and $C_6H_5N_2$ $(M^+ - 105)$. If however, the phenyl substituent is changed for a pyridyl group as in 15, the intermediate nitrilimine undergoes cyclization into the corresponding substituted s-triazolo-(4,3-a)pyridine (16). Here, the slower cycloaddition process is overrun by a faster nucleophilic attack of the ring nitrogen to give the bicyclic product. This has been established also in the case of p-methoxybenzaldehyde 3-nitro-2--pyridylhydrazone (17). Again, no reaction with acrylonitrile could be observed in the presence of lead tetraacetate and the sole product was the triazolopyridine derivative (18). No cycloaddition products could be obtained either from pyridyl-2-aldehyde 6-chloro-3-pyridazinylhydrazone or from p-methoxy-benzaldehyde 2-pyridylhydrazone.

<div style="text-align:center">EXPERIMENTAL</div>

All preparations of intermediates were conducted according to published techniques: pyridyl-2-aldehyde phenylhydrazone, m. p. 183 °C (Lit.[29] gives m. p. 180—182 °C, pyridyl-2-aldehyde-3-nitro-2-pyridylhydrazone m. p. 132—135 °C[30], pyridyl-2-aldehyde 2-pyridylhydrazone, m. p. 185—186 °C (Lit.[31] gives m. p. 179—180 °C).

Pyridyl-2-aldehyde 6-Chloro-3-pyridazinylhydrazone

6-chloro-3-hydrazinopyridazine (2.88 g) was dissolved in hot ethanol (50 ml) and treated with pyridyl-2-aldehyde (2.14 g). The reaction mixture was heated under refluxs for 30 min, cooled, the separated product was filtered off and crystallized from ethanol, m. p. 214—215 °C.

Mass spectrum: $M^+ = 233$.

$Anal.$ $C_{10}H_8ClN_5$ (233.66) calc'd: C 51.40; H 3.45; N 29.98%
found: C 51.68; H 3.62; N 30.40%.

In a similar manner was prepared:

p-Methoxybenzaldehyde 3-nitro-2-pyridylhydrazone, m. p. 172—173 °C (from ethanol).
Mass spectrum: $M^+ = 272$.

$Anal.$ $C_{13}H_{12}N_4O_3$ (272.26) calc'd: C 57.35; H 4.44; N 20.58%
found: C 57.20; H 4.56; N 21.01%.

p-Methoxybenzaldehyde 2-pyridylhydrazone, m. p. 170—171 °C (from ethanol).
Mass spectrum: $M^+ = 227$.

$Anal.$ $C_{13}H_{13}N_3O$ (227.26) calc'd: C 68.70; H 5.77; N 18.49%
found: C 68.92; H 5.88; N 18.72%.

Adduct of Pyridyl-2-aldehyde Phenylhydrazone and Dimethyl Acetylenedicarboxylate (12)

A solution of pyridil-2-aldehyde phenylhydrazone (9) (0.99 g) in 1,2-dimethoxy-ethane (10 ml) was treated with dimethyl acetylenedicarboxylate (0.71 g) and the reaction mixture was heated under reflux for 2 hr. The resulting dark solution was evaporated in vacuo and the residual oil crystallized partly upon standing for 1 week. A small quantity of ethyl acetate was added, the crystals were filtered off and crystallized from ethanol (yield 0.21 g, 12%), m. p. 171—172 °C.

Mass spectrum: M^+ 339, NMR (CDCl$_3$): τ = 1.90—2.50 (m, H$_3$, H$_4$, H$_5$) 1.40 (m, H$_6$), 2.25 (m, Ph), 5.92 and 6.33 (s, OMe), 5.20 (s, C=CH), 2.36 (s, N=CH).

$Anal.$ $C_{18}H_{17}N_3O_4$ (339.34) calc'd: C 63.71; H 5.05; N 12.38%
found: C 64.06; H 5.24; N 12.56%.

If ethanol was used as solvent the product was obtained in 26% yield, in methylene chloride and in the presence of some triethylamine the yield was 32%.

Reaction Between Pyridyl-2-aldehyde Phenylhydrazone and Dimethyl Acetylenedicarboxylate in the Presence of Lead Tetraacetate. Formation of (10)

To a solution of pyridyl-2-aldehyde phenylhydrazone (9) (0.99 g) in anhydrous methylene chloride (50 ml) under stirring dimethyl acetylenedicarboxylate (0.71 g) and lead tetraacetate (2.45 g) were added. The reaction mixture was stirred at room temperature for 2 hr, filtered and the solvent evaporated in vacuo. The residual oil was treated with water, some sodium bicarbonate was added and the mixture extracted with methylene chloride. Upon evaporation of the solvent the residual oil was sublimed at 180—190°/4 mm and the crystals obtained were crystallized from benzene and n-hexane, m. p. 202—204 °C. Mass spectrum: $M^+ = 255$. The compound was found to be identical with the product described in the literature[4].

The same compound was obtained from the above hydrazone if this was treated only with lead tetraacetate under conditions as described above, or in the presence of dienophiles, such as methyl acrylate or diethyl maleinate.

Adduct of Pyridyl-2-aldehyde Phenylhydrazone and Acrylonitrile in the Presence of Lead Tetraacetate. Formation of (14)

To hydrazone (9) (0.99 g) in acrylonitrile (60 ml) under stirring lead tetraacetate (2.45 g) was added and the reaction mixture was stirred for 30 min. Some tetraacetate (0.5 g) was added again and the reaction mixture was stirred for further 15 min. The reaction mixture was evaporated in vacuo and the residue treated with water, extracted with ether, the ethereal extracts were washed with water and the solution was evaporated to dryness. The residue crystallized upon standing (yield 0.51 g) and was crystallized from aqueous ethanol, m. p. 123 °C.

Mass spectrum: $M^+ = 248$, M^+—27 (—HCN), M^+—53 (—CH_2=CHCN), and M^+—105 (—$C_6H_5N_2$, NMR (DMSO-d_6): $\tau = 4.20$ (dd, H_5), 6.20 (d, 4—CH_2), 1.70—2.40 (m, $H_{3'},H_{4'},H_{5'}$), 1.25 (m, $H_{6'}$), 2.60 and 2.25 (m, Ph), $J_{4CH, 5CH} = 7.5$ and 8.5 Hz.

Anal. $C_{15}H_{12}N_4$ (248.28) calc'd: C 72.56; H 4.89; N 22.57%
found: C 72.76; H 5.03; N 22.80%.

3-(Pyridyl-2')-s-triazolo(4,3-a)pyridine (16)

To a stirred mixture of pyridyl-2-aldehyde 2-pyridylhydrazone (15) (0.99 g) and acrylonitrile (40 ml) lead tetraacetate (2.44 g) was added portionwise and the reaction mixture was stirred at room temperature for 1 hr. Excess of acrylonitrile was evaporated in vacuo, to the residue water was added and the mixture was extracted with chloroform. The extracts were washed with water and evaporated to dryness in vacuo. Upon standing the oily residue crystallized and after sublimation at 100—110 °C the product was crystallized from n-heptane (yield 0.3 g, 31%), m. p. 125 °C.

Mass spectrum: $M^+ = 196$. The product was found to be identical with an authentic specimen[30].

3-p-Methoxyphenyl-8-nitro-s-triazolo(4,3-a)pyridine (18)

To a solution of the hydrazone 17 (0.91 g) in acrylonitrile (60 ml) lead tetraacetate (1.62 g) was added portionwise under stirring. After 30 min. some more lead tetraacetate (0.5 g) was added and stirring was continued for 15 min. The reaction mixture was evaporated in vacuo and poured into water and extracted with ether. The ethereal extracts were washed with water, dried, the solvent was evaporated and the residue was extracted with chloroform. The solvent was evaporated and the residue was sublimed at 150—200 °C and crystallized from ethanol (yield 0.15 g, 17%), m. p. 235—240 °C.

Mass spectrum: $M^+ = 270$. NMR (DMSO-d_6, 85 °C): $\tau = 0.82$ (dd, H_5), 2.73 (dd, H_6), 1.47 (dd, H_7), 1.90 (d, $H_{2'},H_{6'}$), 2.96 (d, $H_{3'},H_{5'}$), 6.12 (s, OMe), $J_{2'3'} = 8.5$ Hz.

Anal. $C_{13}H_{10}N_4O_3$ (270.24) calc'd: C 57.77; H 3.73; N 20.73%
found: C 58.04; H 4.00; N 20.98%

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IZVLEČEK

Heterocikli. CLVII. Oksidativne pretvorbe nekaterih heterocikličnih hidrazinov s svinčevim tetraacetatom

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Opisane so reakcije hidrazonov heterocikličnih aldehidov s svinčevim tetra-acetatom ob prisotnosti ali odsotnosti dienofilov. Ugotovili smo, da pri reakciji s svinčevim tetraacetatom vmesno nastali nitrilimini prednostno reagirajo z vezavo acetatnega iona, ne da bi potekla reakcija z acetilenskim dienofilom. Izjema je le akrilonitril, s katerim nastane cikloadukt. V kolikor je struktura vmesnega nitrilimina taka, da lahko pride do dipolarne cikloadicije s piridinovim atomom dušika, nastane triazolopiridin.

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