

Triazolines **24**. Permanganate-Catalyzed Low Temperature Thermolysis of 5-(4-Pyridyl) Substituted 1,2,3-Triazolines [1]
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Dedicated to the memory of Dr. Roland K. Robins

Potassium permanganate oxidation of 1-aryl-5-(4-pyridyl)-1,2,3-triazolines **I** in a benzene-water two-phase system using the phase-transfer catalyst tetrabutylammonium chloride yields the corresponding 1*H*-1,2,3-triazoles **II**. However, when the reaction is run in a single phase in anhydrous benzene alone, the products are not triazoles, but imines **III** that can normally be obtained only by high-temperature thermolysis of the triazolines. The presence of both potassium permanganate and tetrabutylammonium chloride to yield the benzene soluble tetrabutylammonium permanganate ion pair appears essential for imine formation, although only in catalytic amounts. Thus a reaction pathway is proposed, which involves the initial coordination of the pyridyl nitrogen with the manganese atom of the permanganate ion leading to **IV**, followed by loss of nitrogen and regeneration of the permanganate ion *via* the dihydropyridine intermediates, **V** and **VI**, to yield the enamine **VII**, which tautomerizes to the imine **III**. Supportive evidence for the formation of **IV** is derived from the failure of 1,5-diaryl- and 1-aryl-5-(3-pyridyl)triazolines to yield the respective imines; they lack the structural requirements necessary to comply with the proposed mechanism, and are recovered unchanged. Unlike the high temperature pyrolysis, the permanganate catalyzed low temperature thermolysis reactions provide cleaner products in better yields. Thus, the low temperature thermolysis may afford a route for the synthesis of clean samples of 1-arylimino-1-ethyl-4-pyridines, especially when the triazolines are on hand.

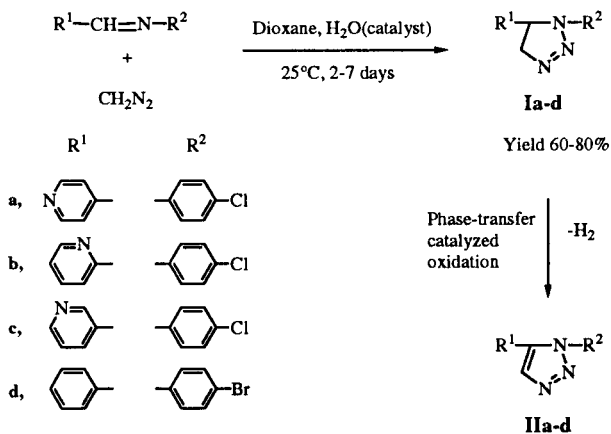
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Introduction.

Although there is an abundance of 1,2,3-triazoline chemistry [2], that of the heterocyclic substituted triazolines [3] is still being unravelled [4-7]. Heterocyclic substituted 1,2,3-triazolines undergo oxidation to heterocyclic substituted 1*H*-1,2,3-triazoles with potassium permanganate in a benzene-water two phase system in the presence of a phase transfer catalyst, tetrabutylammonium chloride [4,5,8] (Scheme I). However, when these reactions are run in a single phase in anhydrous benzene alone, the products formed from the 5-pyridyl substituted triazolines are

not triazoles. While the 5-(4-pyridyl) compounds yield the respective imines (Reaction B, Scheme II), the 5-(3-pyridyl) compounds remain unchanged; a triazole is obtained only from the 5-(2-pyridyl)triazoline, although in highly insignificant amounts. We postulate a permanganate-catalyzed low temperature thermolysis reaction as the underlying pathway for imine formation resulting from 5-(4-pyridyl) substitution. This is the first report where a triazoline thermolytic decomposition has been found to be catalyzed by permanganate, and provides a new entry to the chemistry of heterocyclic substituted 1,2,3-triazolines.

Scheme I



Results and Discussion.

In order to investigate the reaction pathways by which imine *versus* triazole formation occurs, several experiments were conducted using a representative triazoline **Ia** as shown in Scheme II. Reaction of **Ia** with excess potassium permanganate and catalytic amounts of tetrabutylammonium chloride, similar to that used in the phase-transfer reaction (Reaction A) but without the water (Reaction B) yielded 42% of a product that was characterized as the imine **IIIa** (Run #1, Table I) from its elemental analysis, pmr and ir spectra, which were all identical to that of an authentic sample derived from triazoline **Ia** by known thermolytic decomposition reactions (Reaction D) [2].

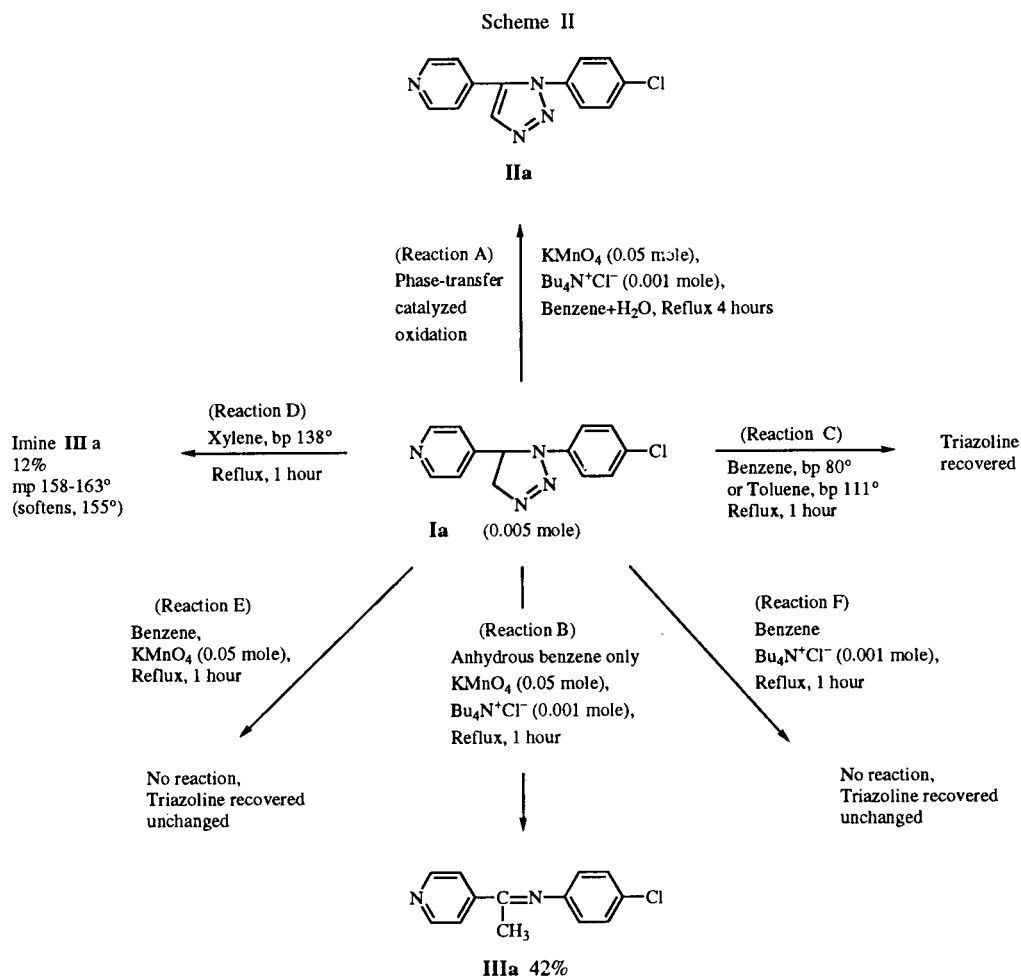


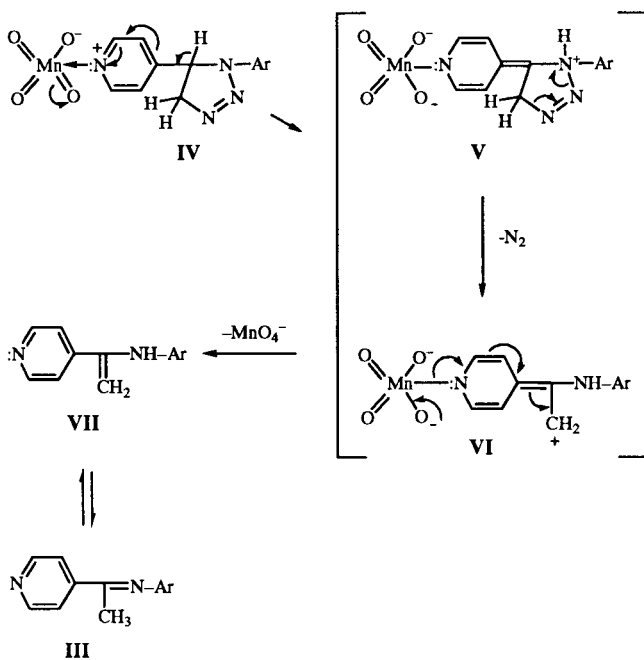
Table I
Thermolysis Reactions of Triazolone (**Ia**) (0.005 mole) to yield **IIIa**, Using Different Amounts of Potassium Permanganate and Tetrabutylammonium Chloride in Benzene (100 ml)

Run #	KMnO ₄ (mole)	Bu ₄ N ⁺ Cl ⁻ (mole)	Reflux- Time, hour (s)	Imine, IIIa , Yield % [a]	Mp °C [a]	PMR (CDCl ₃ /TMS) δ, $\begin{array}{c} \text{C}=\text{N}- \\ \\ \text{CH}_3 \end{array}$ (s)
1	0.054	0.0014	2	42	161-164, softens at 158	
2	0.005	0.005	1	17	161-163, softens at 159	
3	0.013	0.0007	2	42	161-162.5	
4	0.013	0.0007	1	33	161-163, softens at 158	
5	0.013	0.0007	1 [b]	0	-----	
6	0.002	0.0014	1	58	161-163, softens at 159	
7	0.001	0.0007	1	58	161-163 no softening	
8	0.0007	0.0007	1	52	161-164 no softening	2.24
9	0.0007	0.0007	21 [c]	21	153-161	

[a] Melting points and yields are for the crystallized products. [b] When reaction was conducted in CHCl₃, there was no imine formation and the triazolone was recovered unchanged. [c] Reaction was carried out at room temperature.

The boiling temperature of benzene or toluene by itself was not high enough to cause any degree of thermolysis of **Ia** (Reaction C); even xylene (bp 138°) afforded only 12% of a crude sample of **III**, mp 155-163° (Reaction D). Addition of either potassium permanganate or tetrabutylammonium chloride by itself also did not bring about any reaction (Reactions E and F, respectively); imine formation occurred only when both potassium permanganate and tetrabutylammonium chloride were present (Reaction B). In the absence of the quaternary ammonium salt, potassium permanganate is not soluble in benzene, while in its presence, the soluble tetrabutylammonium permanganate ion pair is formed. Thus a reaction pathway in which the permanganate ion coordinates with the triazoline and facilitates its thermolysis at the relatively low temperature of refluxing benzene appeared reasonable. The heteroaromatic nitrogen atom on the 5-(4-pyridyl) ring of **Ia** with its associated high electron density, is a logical site for coordination with the manganese atom *via* its unoccupied *d* orbital. Thus, a reaction involving the initial formation of a triazoline-permanganate coordination complex **IV** may be invoked, followed by loss of nitrogen and regeneration of the permanganate ion *via* the unstable dihydropyridine intermediates, **V** and **VI**, to yield the enamine **VII**, which finally tautomerizes to the stable imine, **III** (see Scheme III).

Scheme III



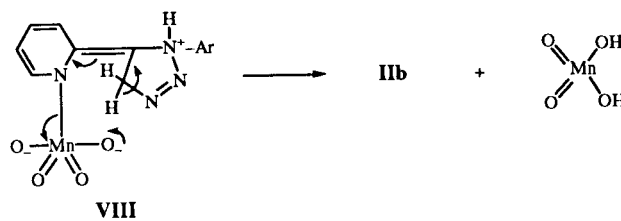
Accordingly, the role of permanganate in Reaction B unlike that in Reaction A (Scheme II) appears to be that of a catalyst that brings about a significant reduction in the high temperature normally required for triazoline ther-

molysis [2] as depicted in Scheme III. Consequently, one might expect that catalytic amounts of tetrabutylammonium permanganate should be sufficient to effect triazoline decomposition leading to imine formation. Indeed, as illustrated in Table I, runs #7 and #8, gave cleaner samples of imine in superior yields. The catalytic role of tetrabutylammonium permanganate in benzene is further apparent from the higher yield of imine resulting from reaction #9 (Table I) conducted at room temperature, compared to that obtained from the pyrolysis reaction in refluxing xylene (Scheme II, Reaction D). In those runs (Table I), where excess potassium permanganate, along with excess or catalytic amounts of tetrabutylammonium chloride was used, product quality as assessed by melting point and yields, were both poor, possibly due to contamination with products arising from further oxidation of the enamine **VII**-imine **III** compounds by excess permanganate.

Further supportive evidence for the formation of the coordination complex **IV** in the proposed reaction pathway (Scheme III) has been obtained from experiments conducted with a 1,5-diaryltriazoline, where the 5-(4-pyridyl) group of triazoline **Ia** is replaced with a phenyl group. If imine formation does indeed involve the coordination of the permanganate with the pyridyl nitrogen, then it is logical to expect no imine formation from the diaryl triazoline **Id** (Scheme I) under the same reaction conditions as those used for **Ia** in run #8 in Table I; in fact, over 70% of the triazoline was recovered unchanged, although under phase-transfer conditions in a benzene-water two-phase system, both **Id** and **Ia** undergo oxidative dehydrogenation [4,5] to yield the respective triazoles, **IId** and **Ia** (Scheme I).

Additional support for the proposed reaction pathway derives from experiments employing 5-(2-pyridyl)- and 5-(3-pyridyl)-substituted triazolines, **Ib** and **Ic**, respectively. If, as postulated in Scheme III, the reaction of **Ia** to yield an imine does indeed proceed *via* the dihydropyridine intermediates **V** and **VI**, this would imply that only triazolines bearing the appropriate 5-(4-pyridyl)- or 5-(2-pyridyl)-, **Ia** and **Ib**, substituents that are capable of leading to such intermediates can yield an imine; in the case of 5-(3-pyridyl)triazoline, **Ic**, where a dihydropyridine intermediate equivalent to **V** and **VI** in Scheme III cannot be formed, no imine will be obtained. Indeed, 60% of pure **Ic** was re-

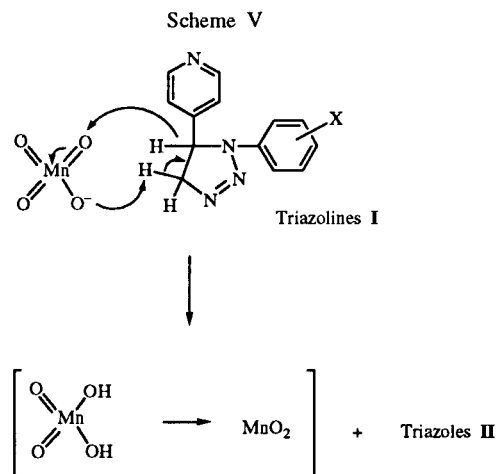
Scheme IV



covered unchanged from a reaction conducted in an identical manner to that described for **Ia**, run #8, Table I.

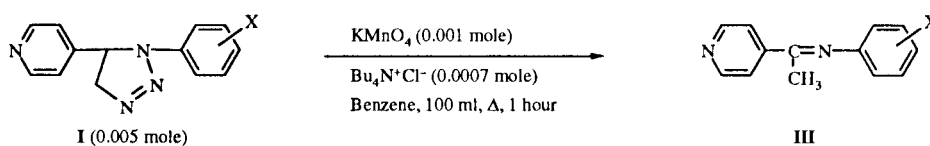
Although in theory, **Ib** should have yielded a 2-pyridylimine, none could be detected; the reaction product from **Ib**, unlike that from **Ia**, was a dark brown oil, which solidified with difficulty to a semiviscous mass. Analysis (tlc) of the latter suggested the presence of triazole **IIb**, which was subsequently isolated in 7% yield as a brownish powder, mp 82-85° (lit mp 90-91° [4]). Analysis (pmr) confirmed the material to be **IIb** mixed with about 27% of the triazoline, **Ib**. Failure of **Ib** to yield an imine, however, does not rule out the formation of the dihydropyridine intermediate **VIII**, because triazole formation from **Ib** could be envisioned only *via* **VIII**, as illustrated in Scheme IV. It is possible that the proximity of the 4-CH₂ of the triazoline to the permanganate moiety in **VIII** initiates a rapid proton abstraction leading to aromatization; this process presumably precludes the decomposition of **VIII** with loss of nitrogen to give the 2-pyridyl analogue of **VI** in Scheme III. Thus the reaction of **Ib** to give **IIb** does not seem to be permanganate-catalyzed and may account for the low yield of **IIb** in a reaction where only catalytic amount of tetrabutylammonium permanganate was used as in run #8, Table I. It is also possible that the failure to detect any imine in the reaction involving **Ib** may be due to the inherent instability of 2-pyridyl compounds in general, including the 2-pyridylimine **IIIb**; in fact, a sample of **IIIb** prepared *via* an unpublished route

readily undergoes decomposition to a dark oil during isolation.



The reaction pathway for triazoline oxidation in the phase-transfer catalyzed reaction is apparently quite different from that for imine formation; dehydrogenation to triazole probably involves interaction of the C-4 and C-5 hydrogens with two sites on the permanganate, and may occur at the benzene-water interface (Scheme V). The abstraction of a proton from C-4 by the negatively charged oxygen greatly facilitates the hydrogen on C-5 to leave with its electron pair, similar to the hydride shift in the Cannizzaro reaction [9]. In fact, during the phase-transfer

Table II



Compound No.	X	Yield, % [a]	Mp °C	PMR (CDCl ₃ /TMS) δ, $\begin{array}{c} \text{C}=\text{N}- \\ \\ \text{CH}_3 \end{array}$ (s)	Analysis		
					C	Calcd./Found H	N
IIIa	4-Cl	52	161-164	2.24	67.67	4.81	12.14
					67.99	4.65	12.20
IIIe	4-Br	45	162-165	2.24	56.72	4.04	10.18
					57.01	4.02	10.20
III f	4-F	35	133-135	2.25	72.87	5.18	13.08
					72.92	5.01	13.12
IIIg	3-Cl	30	80-82.5	2.25	67.67	4.81	12.14
					68.01	4.79	12.16
IIIh	3,4-Cl ₂	40	102-104	2.25	58.88	3.81	10.57
					58.58	3.61	10.47
IIIi	4-CH ₃	32	80-82	2.25	79.95	6.72	13.22
					80.20	6.70	13.41
IIIj	H	30	81-84	2.24	79.55	6.17	14.28
					79.65	6.01	14.26

[a] Yields are for the crystallized, pure products.

catalyzed oxidation of **Ia** in a benzene-water system, when the aqueous-to-organic phase ratio was less than 2:1, imine **III** was formed as a minor side product [7]. Furthermore, the resistance to permanganate oxidation observed in triazolines bearing sterically crowded groups in the 5-position [6,7], lends added support to the proposed reaction in Scheme V.

Although triazoline thermolysis reactions are known to yield imines **III**, in general, they are mixed with other products such as aziridines which make it difficult to purify them, and the yields are too low to have any practical synthetic value [2]. The 1-aryl-5-(4-pyridyl)-1,2,3-triazolines, for example, undergo thermolysis only at temperatures around 150° with imine formation in yields much less than 15% (Reaction D, Scheme II). However, at the low refluxing temperature of benzene in the presence of catalytic amounts of tetrabutylammonium chloride and potassium permanganate, imines ranging in yields from 30-58% can be obtained from these triazolines (Table II).

Unlike the high temperature pyrolysis, the permanganate catalyzed low temperature thermolysis reactions provide cleaner products in better yields. The triazoline starting materials are readily accessible by the Kadaba procedure developed in our laboratories, which involves the water-catalyzed regio-specific 1,3-cycloaddition of diazomethane to Schiff bases (aldimines) [2,3,10-12] (Scheme I). Thus, the low temperature thermolysis may afford a route for the synthesis of clean samples of 1-arylimino-1-ethyl-4-pyridines, especially when the triazolines are on hand and other routes involving the condensation of 4-acetylpyridine with anilines are not readily available.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and were not corrected. The pmr spectra were run on a Varian XL-300 300 MHz spectrometer in deuteriochloroform solutions with TMS as the internal standard. Carbon, hydrogen and nitrogen elemental analyses were performed by Galbraith Laboratories, Knoxville, TN.

Tetrabutylammonium Permanganate-Catalyzed Low Temperature Thermolysis of 1-Aryl-5-(4-pyridyl)-1,2,3-triazolines (Reaction B, Scheme II).

To a solution of the 1-aryl-5-(4-pyridyl)-1,2,3-triazoline **Ia** (0.005 mole) in reagent-grade anhydrous benzene (100 ml) were added powdered potassium permanganate (certified ACS grade, Fisher Scientific) and tetrabutylammonium chloride (95%, Sigma) in specified amounts, and the mixture refluxed with magnetic stirring for different periods as shown in Table I. The reaction mixture was then allowed to cool to room temperature and treated with an aqueous solution of sodium sulfite (10%) to destroy any remaining potassium permanganate. The precipitated dark brown manganese dioxide was filtered under suction and washed with benzene. The benzene layers from the combined filtrates were then washed with water, dried, and rotary

evaporated to a volume of 5-10 ml. Addition of petroleum ether followed by cooling yielded the imine **IIIa**; recrystallization from acetone-petroleum ether mixture gave shining, pale yellow to tannish crystals, with melting points, and yields as given in Table I.

Synthesis of 1-Arylimino-1-ethyl-4-pyridines **IIIe-j**.

Using the reaction conditions of Run #7, in Table I, imines **IIIe-j** were synthesized from the respective triazolines **Ie-j**. The results are presented in Table II.

The pmr spectra of the imines **IIIa** and **IIIe-j** gave, in addition to the characteristic $\text{CH}_3\text{-C=N-}$ singlet signal (Tables I and II), all the expected signals for the pyridyl (δ 8.70-8.8, 2H, δ 7.78-7.80, 2H), phenyl (δ 7.0-7.4, 2H, δ 6.7-6.8, 2H), and the CH_3 on the phenyl ring for **IIIi** (δ 2.36, s).

Other Reactions in Scheme II.

Reaction E was worked up in the same manner as Reaction B above.

In the case of Reaction F where no potassium permanganate was used, the sodium sulfite treatment was not necessary. The reaction mixture was washed with water to remove the tetrabutylammonium chloride and the benzene layer dried and rotary evaporated to yield the product.

Reaction C, after completion, was subjected directly to rotary evaporation and the residual oily material was treated with petroleum ether and cooled, to give the unreacted triazoline.

Reaction D yielded a dark brown mixture which was treated with norit and filtered. The dark filtrate was rotary evaporated and to the dark oily residue petroleum ether was added. The brown precipitate was recrystallized twice to yield the product.

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