1*H*-IMIDAZOLE PREPARATION VIA PERMANGANATE DEHYDROGENATION OF 2-IMIDAZOLINES

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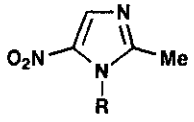
Abstract- Permanganate and manganate ions were evaluated as dehydrogenating agents in the conversion of 2-substituted 2-imidazolines into the corresponding 2-substituted imidazoles. It was found that permanganate ion [Mn(VII)] in dry dioxane efficiently performs this transformation rendering this method competitive with related procedures.

A variety of conditions have been described to oxidize the imidazoline system to imidazole.[1] Indeed some of them are harsh ones that would not allow the survival of certain functional groups in the imidazole ring (Zn-Al_2O_3 300-600 °C[2] ; Ni, 300 °C[3]). Potassium amide has been used to dehydrogenate amarine (2,4,5-triphenylimidazoline) to lophine (2,4,5-triphenylimidazole).[4] Recently Pd/C has been shown to dehydrogenate 2-imidazolines and 2,4-disubstituted imidazolines to imidazoles.[5]

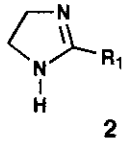
Manganese derivatives such as manganese oxide [Mn(IV)] have been shown to oxidize indolines to indoles[6] and an activated 1,4-disubstituted imidazoline to imidazole.[7] Barium manganate [Mn(VI)] has been applied to dehydrogenate

limited examples of 2-arylimidazolines to 2-arylimidazoles.[8] No reports were found related to the use of permanganate [Mn(VII)] in the oxidation of 2-imidazolines to 1*H*-imidazoles.

We were interested in oxidizing 2-alkylimidazolines to the corresponding 2-alkylimidazoles in an efficient and economic way due to the importance of the latter compounds as synthetic intermediates of valuable nitroimidazole drugs such as metronidazole (**1a**), dimetridazole (**1b**) or tinidazole (**1c**). A comparative study was then undertaken to evaluate oxidation of 2-imidazolines by the different oxidation states of manganese ion.



1	**R**
a	$-CH_2CH_2OH$
b	-Me
c	$-CH_2CH_2SO_2Me$



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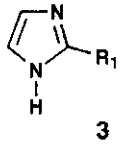
	R_1
a	- Me
b	- Et
c	- Pr



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The required 2-alkylimidazolines (**2a-c**) were prepared by heating acyl ethylenediamines in the presence of magnesium powder, following Chitwood procedure.[9]

When imidazolines (**2a-c**) were treated with barium manganate(VI) in dichloro methane in accordance with experimental conditions of reference 8, they remained unchanged probably due to a lower reactivity of these compounds. Other solvents which included dichloroethane, carbon tetrachloride were tried unsuccessfully. Dry dioxane was proved a suitable solvent to effect the dehydrogenation reaction with barium manganate(VI) of **2a-c** to 2-imidazoles

(**3a-c**) in the yields shown in Table 1. However barium manganate although a powerful oxidizing agent, is also a very toxic substance, therefore we decided to carry out the oxidation of imidazolines (**2a-c**) with *manganese*(V) ion generated *in situ* from formic acid and $KMnO_4$.[10] Thus 2-alkylimidazolines (**2a-c**) were dissolved in formic acid, then $KMnO_4$ was gradually added, CO_2 evolution was observed but we can only assume that Mn(V) is the actual oxidizing species since no further proof was made for its existence.

Dehydrogenation proceeded well giving 2-alkylimidazoles in yields shown in Table 1. Noteworthy is the good yield obtained with 2-ethylimidazoline as compared to the low yield given by 2-methylimidazoline. This latter compound is highly hygroscopic and probably hydrolysis turned out to be the main reaction.

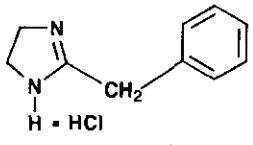
Oxidation of **2a-c** was also performed with manganese(IV) oxide. This was first activated[11] and reaction was tried in different solvents. In CCl_4 oxidation reaction took place but delivered an impure product making the procedure unpractical. Dry dioxane gave better results and 2-alkyl imidazoles (**3a-c**) were isolated from the reaction in yields shown in the table.

Manganese ions IV, V and VI can all be generated from $KMnO_4$,[12] it would then be advantageous if this latter species could oxidize imidazolines (**2a-c**) as well. Accordingly, 2-imidazolines (**2a-c**) were treated directly with an excess of $KMnO_4$ in dioxane for an average of 12 h. Reaction mixture remained heterogenous and gradually MnO_2 was formed, imidazoles (**3a-c**) were isolated in yields shown in Table 1. Although reaction conditions in this case would appear neutral, this is not strictly so, since 2-imidazolines being cyclic amidines do possess certain basicity,[1] making the reaction medium slightly basic.

Table 1

Dehydrogenation Reaction of 2-Alkylimidazolines to 2-Alkylimidazoles with Different Oxidation States of Manganese Ion						
Entry (from)	Mn(VII) Yield of **3**, (%)	Mn(VI) Yield of **3**, (%)	Mn(V) Yield of **3**, (%)	Mn(IV) Yield of **3**, (%)	mp **3**, °C	lit. mp **3**, °C
2a	72.0	68.0	22.3	67.0	142-144	140-141[13]
2b	48.2	52.0	90.3	40.9	83-86	85-86[14]
2c	50.3	49.7	50.5	54.0	158-160	159-161[14]

$KMnO_4$ in dioxane was then applied to dehydrogenate tolazoline hydrochloride (**4**), however no reaction took place. Addition of an excess of base (NaOAc) to allow reaction on the free base and make the reaction medium basic did permit the oxidation to occur, although the benzylic portion was oxidized as well probably <u>via</u> oxygen transfer from permanganate ion. 2-Benzoylimidazole (**5**) was isolated in 42% yield (mp 169-170 °C, m/z 172),[15] instead of the expected 2-benzylimidazole (**6**).[5] Attempted oxidation of **4** with barium manganate(VI) or formic acid/$KMnO_4$ led only to untractable material.



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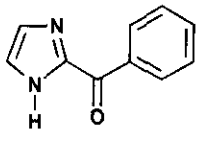

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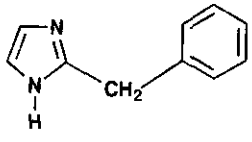

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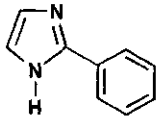

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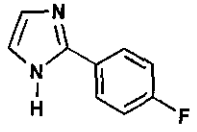

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The combination $KMnO_4$/dioxane oxidized 2-phenylimidazoline and 2-(4-fluoro phenyl)imidazoline (prepared from benzonitrile and 4-fluorobenzonitrile through the corresponding iminoester hydrochloride)[16] to 2-phenylimidazole (**7**) (mp 147-148 °C)[17] and 2-(4-fluorophenyl)imidazole (**8**) (mp 195-197 °C)[18] in 40 and 38% yield respectively.

Thus we conclude that dehydrogenation of 2-imidazolines is possible with permanganate [Mn(VII)] ion using dry dioxane as solvent. The method, quite simple to perform in the laboratory, represents a practical alternative to obtain 1*H*-imidazoles.

EXPERIMENTAL

Melting points were measured on a electrothermal melting point apparatus and are uncorrected. Ir spectral data were obtained using a Perkin Elmer FT 1600 infrared spectrophotometer. ^1H Nmr spectral data were obtained using a Varian A-60A (60 MHz) nmr spectrometer. Mass spectrum was obtained with a Hewlett Packard Vectra 486S/20 instrument. Column chromatography was carried out with silica gel (Merck 60, 70-230 mesh) as the adsorbent. Dioxane was dried with sodium under nitrogen and distilled prior to use.

2-Imidazoline dehydrogenation with permanganate(VII) ion.

2-Methylimidazole (3a). 2-Methyl-2-imidazoline (0.5 g, 5.95 mmol) was dissolved in dry dioxane (15 ml), under an inert (N_2) atmosphere. $KMnO_4$ (1.5 g, 9.5 mmol) was added to the solution in small portions, with stirring. Reaction mixture was then refluxed during 12 h. Then it was allowed to cool to ambient temperature and filtered through Celite. Solvent was removed under reduced pressure to leave a yellowish solid, which was recrystallized from toluene to give the title compound (352 mg, 72 %) mp 140-142 °C (lit.,[13] 140-141 °C).

2-Ethylimidazole (3b). Obtained in 48.2% from 2-ethyl-2-imidazoline, following the procedure described above, mp 84-86 °C (lit.,[14] 85-86 °C).

2-Propylimidazole (3c). Obtained in 50.3% from 2-propylimidazoline following the procedure described above and after column chromatography percolation on silica gel (8:2 benzene/$CHCl_3$), mp 155-157 °C (lit.,[14] 159-161 °C).

2-Imidazoline dehydrogenation with manganate(V) ion .

2-Methylimidazole (3a). 2-Methyl-2-imidazoline (0.5 g, 5.95 mmol) was dissolved in 90% HCOOH (11 ml). Solution was cooled to 0 °C. $KMnO_4$ (1.5 g, 9.5 mmol) was added in small portions such that reaction temperature did not exceed 5 °C. After addition was completed, reaction mixture was allowed to reach room temperature and refluxed for 10 h. It was then allowed to cool to ambient temperature and filtered through Celite. Formic acid was distilled off under reduced pressure, the residue taken in EtOAc was succesively washed with 1 N NaOH (1 x 10 ml) and water (1 x 10 ml). Solvent was dried (Na_2SO_4) and removed under vaccum. Solid obtained was recrystallized from benzene to give title compound (116 mg, 22.4%), mp 141-143 °C (lit.,[13] 140-141 °C).

2-Ethylimidazole (3b). Obtained in 90.3% from 2-ethyl-2-imidazoline with HCOOH / $KMnO_4$ following the procedure described above, mp 84-85 °C (lit.,[14] 85-86 °C).

2-Propylimidazole (3c). Obtained in 50.5% from 2-propyl-2-imidazoline and HCOOH / $KMnO_4$ following the procedure described above, mp 155-157 °C (lit.,[14] 159-161 °C).

2-Imidazoline dehydrogenation with manganate(VI) ion.

2-Methylimidazole (3a). To a solution of 2-methyl-2-imidazoline (0.5 g, 5.95 mmol) in dry dioxane (15 ml) was added in portions $BaMnO_4$ (1.9 g, 7.77 mmol) with stirring and under an inert (N_2) atmosphere. Reaction mixture was refluxed during 12 h. It was then cooled to room temperature and filtered through Celite, solvent was removed under reduced pressure and the solid

obtained was recrystallized from toluene to yield title compound (332 mg, 68%), mp 140-142 °C (lit.,[13] 140-141 °C).

2-Ethylimidazole (3b). Obtained in 52% from 2-ethyl-2-imidazoline and $BaMnO_4$ following the procedure described above, mp 84-85 °C (lit.,[14] 85-86 °C).

2-Propylimidazole (3c). Obtained in 49.7% from 2-propyl-2-imidazoline following the procedure described above, mp 155-157 °C (lit.,[14] 159-161 °C).

2-Imidazolines dehydrogenation with manganese(IV) ion.

2-Methylimidazole (3a). To a solution of 2-methyl-2-imidazoline (0.5 g, 5.95 mmol) in dry dioxane (15 ml), activated MnO_2[10] (1.5 g, 17.25 mmol) was added with stirring and under nitrogen atmosphere. Work up of the reaction as previously described gave the title compound (327 mg, 67%), mp 143-144 °C (lit.,[13] 140-141 °C).

2-Ethylimidazole (3b). Obtained in 40.9% from 2-ethylimidazoline and MnO_2, following the above procedure, mp 85-86 °C (lit.,[14] 85-86 °C).

2-Propylimidazole (3c). Obtained in 54% from 2-propylimidazoline and MnO_2, following the above procedure, mp 159-160 °C (lit.,[14] 159-161 °C).

2-Benzoylimidazole (5). Under a blanket of nitrogen, tolazoline hydrochloride (300 mg, 1.52 mmol) and sodium acetate (300 mg, 3.65 mmol) were stirred in dioxane (30 ml) at room temperature until turbidity was negligible. $KMnO_4$ (900 mg, 5.7 mmol) was added in portions, then the reaction mixture was refluxed for 24 h. The heterogeneous mixture was cooled and filtered through Celite. Solvent was removed under reduced pressure to leave a brownish solid which was purified by column chromatography (80:20 hexane/ethyl acetate) to give the title compound as yellow crystals (110 mg, 42%), mp 167-167.5 °C (lit.,[15] 161-162 °C). Ir (KBr, νmax) 3100, 1650, 1600. ^{1}H Nmr (DMSO-d_6) δ: 7.3-7.6 (m, 6 H), 8.5-8.8 (m, 2H). Ms: m/z 172 (M^+), 144 (M^+- CO), 105 ($PhCO^+$).

2-Phenylimidazole (7). To a solution of 2-phenyl-2-imidazoline (250 mg, 1.71 mmol) and sodium acetate (300 mg, 3.65 mmol) in dry dioxane (30 ml), $KMnO_4$ (800 mg, 5 mmol) was added portionwise and the resultant mixture was refluxed for 16 h. Then it was permitted to cool to room temperature and filtered through Celite. Solvent was removed under reduced pressure, residue was taken in ethyl acetate (20 ml) and succesively washed with 1 N NaOH (1 x 10 ml) and water (1 x 10 ml). Solvent was dried over $MgSO_4$ and removed under vacuum. Crude material was filtered through silica gel (2:1 hexane/ethyl acetate) to give the title compound (98 mg, 40%), mp 147-148 °C (lit.,[17] 148-149 °C).

2-(4'-Fluorophenyl)imidazole (8). Obtained in 38% from 2-(4-fluorophenyl)-2-imidazoline, following a similar procedure as described above, mp 195-197 °C (lit.,[18] 196-198 °C).

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