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SYNTHESIS OF IMIDAZOLE DERIVATIVES FROM α-HALOOXIMES AND AMIDINES BY USE OF IRON CARBONYLS

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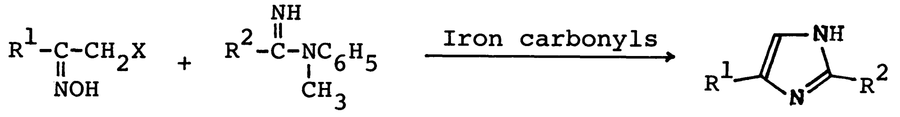
The reaction of α-halooximes with amidines in the presence of iron carbonyls gives imidazole derivatives in good yields. This reaction occurs via deoxygenation of 4H-1,2,5-oxadiazines by iron carbonyls.

Iron carbonyls induce a variety of organic transformations.[1)] They can be utilized even for heterocyclic transformations. For example, azirines can be converted into other heterocycles such as pyrroles,[2,3)] pyridines[3)], pyrazines[4)] and isoxazoles,[4)] depending on the structures of azirines and iron carbonyls employed. However, the selectivity in these transformations is not so high that several compounds are usually produced as by-products. Previously, we have shown that 5,6-dihydro-4H-1,2-oxazines, which are accessible from α-bromooximes and enamines, are converted selectively into pyrrole derivatives in high yields by deoxygenation with $Fe_3(CO)_{12}$.[5)] We now report the synthesis of imidazole derivatives from α-halooximes and amidines by use of iron carbonyls as a deoxygenating agent.



1 2 3

A mixture of α-bromoacetophenone oxime (1a, 1.0 mmol) and N-methyl-N-phenylbenzamidine (2a, 5.0 mmol) in 1,2-dichloroethane (DCE, 20 ml) was stirred at room temperature for 4 h. $Fe_3(CO)_{12}$ (2.0 mmol) was added and the resulting mixture was heated at 80°C for 20 h. After adding silica gel (5g), the mixture was filtered and the filtrate was evaporated. The residue was chromatographed on silica gel with benzene-ethyl acetate (4:1) to give 2,4-diphenylimidazole (3a) in 74 % yield together with a 64 % recovery of the benzamidine used.

Similar treatment of a mixture of α-halooximes (1a-f) and aromatic amidines (2a-b) with $Fe_3(CO)_{12}$ yielded the corresponding imidazole derivatives (3a-f). The results are summarized in Table 1.

In these transformations, excess amidines were always needed in order to obtain the imidazoles in high yields although substantially all the unreacted amidines (>80%) were recovered by chromatography from the reaction mixtures.

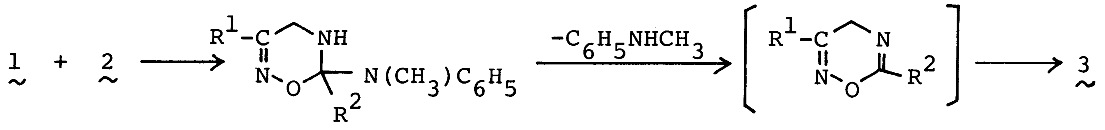
Table 1. Reaction of α-halooximes with amidines in the presence of $Fe_3(CO)_{12}$

Oxime			Amidine		Imidazole	
1	R^1	X	**2**	R^2	**3**	Yield, %[a)]
1a	C_6H_5	Br	**2a**	C_6H_5	**3a**	74
	C_6H_5	Br	**2b**	$m\text{-}CH_3C_6H_4$	**3b**	79
1b	C_6H_5	Cl	**2a**	C_6H_5	**3a**	68
1c	$p\text{-}CH_3C_6H_4$	Br	**2a**	C_6H_5	**3c**	69
1d	$p\text{-}BrC_6H_4$	Br	**2a**	C_6H_5	**3d**	73
1e	CH_3	Cl	**2a**	C_6H_5	**3e**	59
1f	C_2H_5OCO	Br	**2a**	C_6H_5	**3f**	31

a) Isolated yields based on oximes used.

No imidazole derivatives were obtained from aliphatic amidines such as N-methyl-N-phenylacetamidine and N-methyl-N-phenylbutamidine. Among iron carbonyls examined, $Fe_3(CO)_{12}$ was most effective for the above transformations; the efficiency of iron carbonyls for these transformations decreased in the following order: $Fe_3(CO)_{12} > Fe_2(CO)_9 > Fe(CO)_5$.[6)]

A possible pathway of the reaction is shown in Scheme 1. α-Halooximes react with amidines to give 5,6-dihydro-4H-1,2,5-oxadiazines (**4**) by elimination of hydrogen halide.[7)] A base-catalyzed elimination of N-methylaniline from **4** affords the corresponding 4H-1,2,5-oxadiazines (**5**).[8)] Finally, the deoxygenation of **5** by iron carbonyls gives the imidazoles.



4 **5** Scheme 1.

References

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6) The reactions of **1a** (1.0 mmol) and **2a** (5.0 mmol) were carried out in the presence of $Fe(CO)_5$ (6.0 mmol), $Fe_2(CO)_9$ (3.0 mmol) and $Fe_3(CO)_{12}$ (2.0 mmol) under similar conditions described in text, giving **3a** in the yields of 54 % for $Fe(CO)_5$, 60 % for $Fe_2(CO)_9$ and 74 % for $Fe_3(CO)_{12}$.
7) Treatment of **1a** with **2a** in DCE at room temperature without added $Fe_3(CO)_{12}$ gave 5,6-dihydro-3,6-diphenyl-4H-6-(N-methylanilino)-1,2,5-oxadiazine **4a** in 51 % yield, mp 134-135°C :IR(KBr) 3280cm^{-1}(νNH); NMR($CDCl_3$) δ=3.10(3H,s,NCH_3) 5.19(2H,d,J=6 Hz, $\underline{CH_2}NH$), 6.5-6.7(1H,m,NH), 6.9-7.9 ppm(15H,m,C_6H_5). Compound **4a** was converted to **3a** by treating with $Fe_3(CO)_{12}$ in 93 % yield.
8) N-Methylaniline was obtained in high yield in all the imidazole-forming reactions.

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