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)} pyridines³⁾, pyrazines⁴⁾ 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 Fe₃(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.



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. Fe₃(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 (la-f) and aromatic amidines (2a-b) with Fe₃(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.

Oxime			Amidine		Imidazole	
1	R ¹	х	2 ~	R ²	3~	Yield, ^{%^{a)}}
la ∼	с ₆ н ₅	Br	2a	C ₆ H ₅	3a ≁	74
	с ₆ н ₅	Br	$\overset{\mathrm{2b}}{\sim}$	m-CH ₃ C ₆ H ₄	3b ≈	79
$\overset{\text{lb}}{\sim}$	^С 6 ^Н 5	C1	2a ~	с ₆ н ₅	3a ≫	68
lc ≈	p-CH ₃ C ₆ H ₄	Br	2a ∼	с ₆ н ₅	3c ≁	69
1₫	p-BrC ₆ H ₄	Br	2a	с ₆ н ₅	3d	73
le	CH ₃	Cl	2a ≈	C ₆ H ₅	3e	59
lf	C ₂ H ₅ OCO	Br	2a ≁	C ₆ H ₅	3£	31

Table 1. Reaction of α -halooximes with amidines in the presence of Fe₃(CO)₁₂

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, $\text{Fe}_3(\text{CO})_{12}$ was most effective for the above transformations; the efficiency of iron carbonyls for these transformations decreased in the following order: $\text{Fe}_3(\text{CO})_{12} > \text{Fe}_2(\text{CO})_9 > \text{Fe}(\text{CO})_5$.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.

$$\begin{array}{c} 1 + 2 \\ \sim \end{array} \xrightarrow{R^{1}-C \\ N \\ N \\ R^{2}} \xrightarrow{N (CH_{3})C_{6}H_{5}} \xrightarrow{-C_{6}H_{5}NHCH_{3}} \left[\begin{array}{c} R^{1}-C \\ N \\ N \\ N \\ O \\ R^{2} \end{array} \right] \xrightarrow{3} \\ Scheme 1. \end{array}$$

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- 6) The reactions of la (1.0 mmol) and 2a (5.0 mmol) were carried out in the presence of Fe(CO)₅ (6.0 mmol), Fe₂(CO)₉ (3.0 mmol) and Fe₃(CO)₁₂ (2.0 mmol) under similar conditions described in text, giving 3a in the yields of 54 % for Fe(CO)₅, 60 % for Fe₂(CO)₉ and 74 % for Fe₃(CO)₁₂.
- 7) Treatment of la with 2a in DCE at room temperature without added Fe₃(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(ν NH); NMR(CDCl₃) δ =3.10(3H,s,NCH₃) 5.19(2H,d,J=6 Hz, CH₂NH), 6.5-6.7(1H,m,NH), 6.9-7.9 ppm(15H,m,C₆H₅). Compound 4a was converted to 3a by treating with Fe₃(CO)₁₂ in 93 % yield.
- 8) N-Methylaniline was obtained in high yield in all the imidazole-forming reactions.

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