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SYNTHESIS OF PYRROLE DERIVATIVES VIA DEOXYGENATION OF 4H-1,2-OXAZINES BY IRON CARBONYLS

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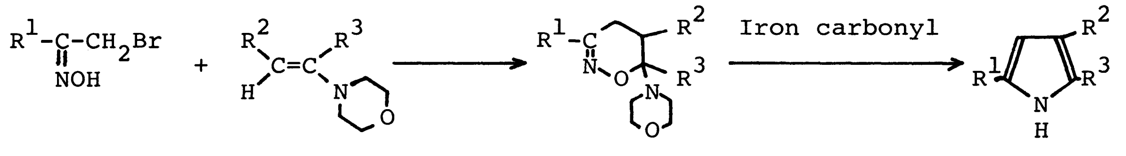
The reaction of 5,6-dihydro-4H-1,2-oxazines, which are derived from α-bromooximes and enamines, with iron carbonyl complexes such as $Fe_3(CO)_{12}$ and $(C_2H_5)_3NH[HFe_3(CO)_{11}]$ gives pyrrole derivatives in high yields, accompaning deoxygenation from the oxazines. The pyrroles are also obtained by an one-pot reaction using α-bromooximes, enamines and iron carbonyls.

Iron carbonyls often induce unique organic transformations. They can be utilized for the deoxygenation of oximes, N-oxides, nitro and nitroso compounds.[1)] One attractive application of this reaction in organic synthesis may be the preparation of nitrogen-containing heterocyclic compounds. We now report a convenient synthesis of pyrrole derivatives by use of iron carbonyls from 5,6-dihydro-4H-1,2-oxazines which can be prepared from the reaction of α-bromooximes with enamines.



1 **2** **3** **4**

A mixture of α-bromoacetophenone oxime (**1a**, 1.5 mmol) and 1-morpholino-1-cyclohexene (**2a**, 3.0 mmol) in toluene (20 ml) was stirred at room temperature for 3 h. The resulting mixture was washed with water, dried ($MgSO_4$), and evaporated. Recrystallization of the residue from ethanol gave 1-morpholino-4-phenyl-2-oxa-3-azabicyclo[4.4.0]dec-3-ene (**3a**) in 91 % yield.

Similar treatment of α-bromooximes **1a,b** with two equiv of enamines **2a-f** gave the corresponding 5,6-dihydro-4H-1,2-oxazines **3a-g** in high yields.[2)] The results are summarized in Table 1.[3)] Aliphatic α-halooximes such as bromoacetone oxime failed to give oxazines.

The oxazines thus obtained reacted with $Fe_3(CO)_{12}$ to give pyrrole derivatives in good yields, accompaning elimination of morpholine and deoxygenation. In a typical example, a mixture of **3a** (1.0 mmol) and $Fe_3(CO)_{12}$ (1.5 mmol) in 1,2-dichloroethane (DCE) (15 ml) was stirred under argon at 80°C for 3 h, and then

Table 1. Formation of 5,6-dihydro-4H-1,2-oxazines

Oxime 1	 R^1	Enamine 2	 R^2	 R^3	Oxazine 3	 Yield,%a)	 mp,°C
1a	C_6H_5	2a	$-(CH_2)_4-$		3a	91	157-159
	C_6H_5	2b	$-(CH_2)_3-$		3b	82	89-91
	C_6H_5	2c	$-(CH_2)_5-$		3c	90	111-112.5
	C_6H_5	2d	C_2H_5	H	3d	80	126.5-128
	C_6H_5	2e	CH_3	C_2H_5	3e	82	106-108
	C_6H_5	2f	CH_3	C_6H_5	3f	78	118.5-120
1b	C_2H_5OCO	2a	$-(CH_2)_4-$		3g	86	73-75.5

a) Isolated yields.

filtered. The filtrate was evaporated, and the residue was chromatographed on silica gel with hexane-benzene (1:1), giving 4,5,6,7-tetrahydro-2-phenylindole (4a) in a quantitative yield.

Similarly, the oxazines 3b-g were converted into the pyrrole derivatives 4b-g. The results are shown in Table 2.3) The yields of 4b and 4g were low. However, their yields were appreciably improved by treating the oxazines with $Fe_3(CO)_{12}$ in DCE in the presence of excess trifluoroacetic acid (Table 2).

Table 2. Reaction of 5,6-dihydro-4H-1,2-oxazines with $Fe_3(CO)_{12}$a)

 3	Oxazine R^1	 R^2	 R^3	 Solvent	 4	Pyrrole Yield,%b)	 mp,°C
3a	C_6H_5	$-(CH_2)_4-$		DCE	4a	99	109-110
				THFc)		98	
				Toluened)		84	
3b	C_6H_5	$-(CH_2)_3-$		DCE	4b	28	121-122
				DCEe)		53	
3c	C_6H_5	$-(CH_2)_5-$		DCE	4c	92	111-112.5
3d	C_6H_5	C_2H_5	H	DCE	4d	85	106.5-108
3e	C_6H_5	CH_3	C_2H_5	DCE	4e	70	105-107
3f	C_6H_5	CH_3	C_6H_5	DCE	4f	58	102-103
3g	C_2H_5OCO	$-(CH_2)_4-$		DCE	4g	16	107-108.5
				DCEe)		55	

a) Oxazine; 1.0 mmol, $Fe_3(CO)_{12}$; 1.5 mmol, Solvent; 15 ml, Reaction temperature; 80°C, Reaction time; 3 h.

b) Isolated yield. c) Reaction temperature; 60°C, Reaction time; 20 h.

d) Reaction temperature; 100°C, Reaction time; 3 h.

e) Trifluoroacetic acid (3.0 mmol) was added.

Other iron carbonyl complexes were also effective for the deoxygenation of the oxazines. The efficiency of the complexes for this reaction decreased in the order: $Fe_3(CO)_{12} \gg (C_2H_5)_3NH[HFe_3(CO)_{11}] > Fe_2(CO)_9 \gg Fe(CO)_5$ (Table 3). However, reducing agents such as Zn (dust) and Zn-CH_3COOH were ineffective for the deoxygenation.

Table 3. Efficiency of iron carbonyls in the deoxygenation of 3a[a)]

Iron carbonyl	mmol	Yield of 4a, %
$Fe_3(CO)_{12}$	1.5	99
$(C_2H_5)_3NH[HFe_3(CO)_{11}]$	1.5	57
$Fe_2(CO)_9$	2.25	49
$Fe(CO)_5$	4.5	trace

a) A mixture of 3a (1.0 mmol) and an iron carbonyl complex in DCE (15 ml) was stirred at 80°C for 3 h.

For the synthesis of pyrrole derivatives, the above two reactions were able to be carried out successively in a single flask: A mixture of an α-bromooxime (1.5 mmol) and an enamine (3.0 mmol) in toluene (15 ml) was stirred at room temperature for 3 h. After adding $Fe_3(CO)_{12}$ (2.25 mmol), the reaction mixture was heated at 100°C for 3 h. Work-up of the resulting mixture gave pyrrole derivatives. The results of the one-pot reactions are given in Table 4. The pyrrole derivatives were obtained generally in good yields by this procedure without adding trifluoroacetic acid. However, for 4g and 4h the addition of the acid improved their yields.

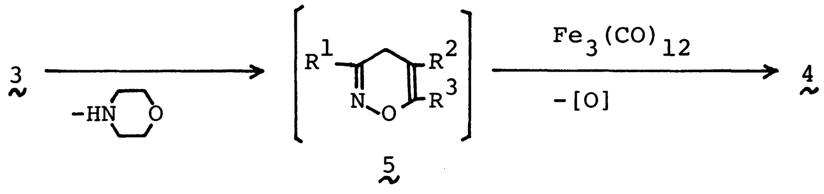
Table 4. Pyrrole synthesis by one-pot reactions using α-bromooximes, enamines and $Fe_3(CO)_{12}$

Oxime		Enamine			Pyrrole	
1	R^1	2	R^2	R^3	4	Yield, %[a)]
1a	C_6H_5	2a	$-(CH_2)_4-$		4a	72
1a		2b	$-(CH_2)_3-$		4b	53
1a		2e	CH_3	C_2H_5	4e	49
1b	C_2H_5OCO	2a	$-(CH_2)_4-$		4g	50[b)]
1b		2e	CH_3	C_2H_5	4h	67[b)]
1c	$p-CH_3C_6H_4$	2a	$-(CH_2)_4-$		4i	61
1d	$p-BrC_6H_4$	2a	$-(CH_2)_4-$		4j	61

a) Isolated yield.

b) The reaction was conducted in DCE at 80°C for 3h in the presence of trifluoroacetic acid (4.5 mmol).

Although the detailed mechanism for the deoxygenation of the oxazines by iron carbonyls is uncertain at present, it is conceivable that the deoxygenation occurs through 4H-1,2-oxazines **5** which are produced by an acid-catalyzed elimination of morpholine from **3**.



References and Notes

1) H. Alper, "Transition Metal Organometallics in Organic Synthesis", ed. by H. Alper, Academic Press, New York (1978), Vol. 2, p 132, and references cited therein.

2) The reactions of α-halooximes with enamines to form oxazines have been studied by Bravo,[a)] and Gilchrist,[b)] and their coworkers: a) P. Bravo, G. Gaudiano, P. P. Ponti, and A. U. Ronchi, Tetrahedron, **26**, 1315 (1970), b) F. Faragher and T. L. Gilchrist, J. Chem. Soc., Perkin I, 249 (1979).

3) The structures of new compounds reported in this paper were secured from their analytical and spectral data.

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