Ethyl 3-Bromo-2-hydroxyiminopropanoate, a Reagent for the Preparation of Ethyl Esters of α-Amino Acids

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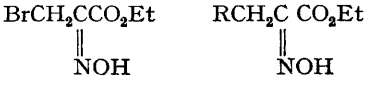
Summary The title compound (**1**) reacts with a variety of nucleophiles in the presence of sodium carbonate to give α-hydroxyimino esters, which can be reduced to α-amino esters.

WE have described the reactions of α-halogeno-oximes with nucleophilic olefins, dienes, and aromatic compounds in the presence of sodium carbonate, and have suggested that these reactions involve cycloaddition or conjugate addition of the nucleophiles to transient nitroso-olefins.[1] We have now applied this type of process to the synthesis of α-hydroxyimino and α-amino esters.



(**1**) (**2**) **a**; R = 3-indolyl
b; R = 2-pyrrolyl
c; R = 1-methyl-2-pyrrolyl
d; R = 4-MeC_6H_4S
e; R = $PhCH_2S$
f; R = $(EtO_2C)_2CH$

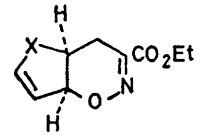
The required reagent, ethyl 3-bromo-2-hydroxyiminopropanoate (**1**), was prepared from ethyl pyruvate in two steps (*ca.* 50% overall yield) by bromination[2] followed by reaction of the bromo-ester in a two phase (chloroform–water) system with hydroxylamine sulphate; it is a crystalline solid, m.p. 76—78 °C. The hydroxyimino ester reacted with a range of nucleophiles in the presence of sodium carbonate. The products were of two types (Table 1).

TABLE 1. Esters formed from ethyl 3-bromo-2-hydroxyiminopropanoate and nucleophiles.[a]

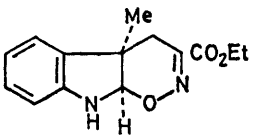
Compound	Yield[b]/%	M.p. (b.p.)/°C
(**2a**)	82	155—157[c]
(**2b**)[d]	55	118—120
(**2c**)[d]	53	98—101
(**2d**)	50	61—62
(**2e**)	53	48—49
(**2f**)	37	(175 at 0·01 mm Hg)
(**3a**)	46	75—77
(**3b**)	79	(135 at 0·08 mm Hg)
(**4**)	81	70—71
(**5**)	46	(160 at 0·05 mm Hg)
(**6**)	100	(175 at 0·005 mm Hg)
(**7**)	43	71—72

[a] Reactions were carried out in dichloromethane at room temperature. The bromo-ester (**1**) was stirred with an excess (2—5 moles) of the substrate in the presence of sodium carbonate. [b] Yields are for isolated compounds. New compounds are fully characterised. [c] Lit.,[3] m.p. 156—157 °C. [d] Contains about 20% of the 3-pyrroyl isomer.

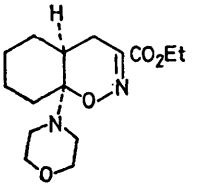
Indole, pyrrole, thiols, and malonate anion gave hydroxyimino esters of the general formula (**2**); furan, 3-methylindole, cyclopentadiene, and nucleophilic alkenes gave cycloadducts (**3**)—(**7**), these cycloadditions being highly regio- and stereo-selective.



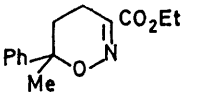
(**3**) a; X = O
b; X = CH_2



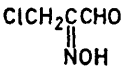
(**4**)



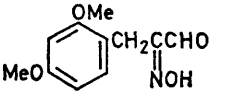
(**6**)



(**7**)

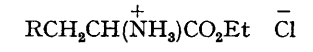


(**8**)



(**9**)

The reaction is limited to good nucleophiles; thus, aromatic systems of slightly lower nucleophilicity such as thiophen and 1,3-dimethoxybenzene failed to give adducts in synthetically useful yields. In order to overcome this limitation we sought to increase the electrophilicity of the intermediate nitroso compounds by introducing a more powerful activating group than the ethoxycarbonyl function. 3-Chloro-2-hydroxyiminopropanal (**8**) is readily available from the addition of nitrosyl chloride to acrolein;[4] this chloro-oxime reacted with 1,3-dimethoxybenzene in the presence of sodium carbonate to give the α-hydroxyiminoaldehyde (**9**) (41%). The aldehyde (**9**) was then successively oxidised to the corresponding acid (silver oxide) and esterified (diazomethane) in good overall yield, thus providing an alternative route to the α-hydroxyimino ester.



(**10**) **a**; R = 3-indolyl
b; R = 2-furyl
c; R = $PhCH_2S$
d; R = 4-MeC_6H_4S

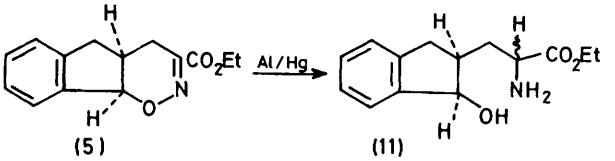
The esters (**2**) can be reduced to the corresponding α-amino esters using aluminium amalgam.[5] The α-amino esters were isolated [as hydrochloride salts (**10**)] in the yields shown in Table 2. Aluminium amalgam is also effective in reducing the cycloadducts; the furan adduct (**3a**) gave the 2-furyl ester (**10b**) but with other bicyclic systems such as the indene adduct (**5**) the reduction is not

TABLE 2. Hydrochlorides of α-amino esters formed by reduction of α-hydroxyimino esters.[a]

Compound	Yield/%	M.p./°C
(**10a**)	96	222—225[b]
(**10b**)	52	139—140
(**10c**)	83	131—132
(**10d**)	89	83—84

[a] Reductions were carried out by heating the oxime with an excess of aluminium amalgam in moist ether under reflux for 7 h. New compounds are fully characterised. [b] Lit.,[6] m.p. 226—227 °C [(±)-tryptophan ethyl ester].

stereoselective; (**5**) gave a mixture of diastereomeric α-amino esters (**11**). The overall process does, however, provide a mild and potentially versatile procedure for the



(5) (11)

conversion of a variety of nucleophilic substrates into α-amino acid derivatives. Recent reports also indicate that α-hydroxyimino acids[7] and esters[8] can be selectively reduced to the corresponding α-hydroxylamino compounds: the routes described here should therefore provide a convenient entry into these classes of compounds.

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