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Ti(IV) MEDIATED TRANSESTERIFICATION AND REGIO- AND STEREO-SPECIFIC CYCLOADDITION OF IMINES OF α-AMINO ESTERS. REVERSAL OF NORMAL REGIOCHEMISTRY.

Darrin A. Barr, Ronald Grigg*† and Visuvanathar Sridharan.

(Chemistry Department, Queen's University, Belfast BT9 5AG, Northern Ireland).

Abstract : $Ti(OPr^i)_3Cl$ or $Ti(OPr^i)_2Cl_2$ in combination with triethylamine effect regio- and stereo-specific cycloaddition of imines of α-amino methyl esters to methyl acrylate at room temperature with reversal of the normal regiochemistry. Transesterification of the imine ester group competes with cycloaddition leading to a mixture of pyrrolidines bearing C(2) methyl and isopropyl ester substituents.

Following our discovery of the facile generation of 1,3-dipoles, $X{=}\overset{+}{Y}(H){-}\overset{-}{Z}$, by thermal 1,2-prototropy in $X{=}\ddot{Y}{-}ZH$ systems[1], we subsequently reported that a combination of metal salt (silver, lithium or zinc) and triethylamine in THF, dipolar aprotic solvents (MeCN, DMSO, DMF) or N-methylacetamide effects rapid regio- and stereo-specific, or highly stereoselective, inter- and intra-molecular cycloaddition of imines of α-amino esters to a range of dipolarophiles.[2] Silver acetate is a more efficient and selective catalyst than lithium bromide and reactions in acetonitrile, DMSO or N-methylacetamide are especially rapid (0.1-3.5 h). Tsuge later reported analogous studies for lithium bromide in THF[3] and, like us, found that lithium bromide shows a tendency to promote Michael addition in addition to, or to the exclusion of, cycloaddition.[4,5] Some transition metal salts such as $MnBr_2$ also effect cycloaddition giving pyrrolidines whilst others, such as $CoCl_2$, give rise to imidazolidines *via* imine dimerisation. Magnesium salts can give rise to either pyrrolidines or imidazolidines depending on the counterion.[6]

We now report related studies with Ti(IV) complexes. When the imine (1a) (1 mol) was reacted (2 h, 25°C) with methyl acrylate (2 mol) in dry THF in the presence of $Ti(OPr^i)_3Cl$ (1.5 mol) and triethylamine (1 mol) reaction occurred to give a *ca.* 1.4 : 1 mixture

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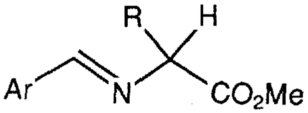
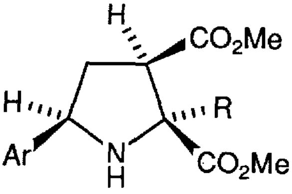
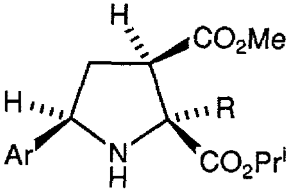
†Present address : School of Chemistry, University of Leeds, Leeds, LS2 9JT.



(1)

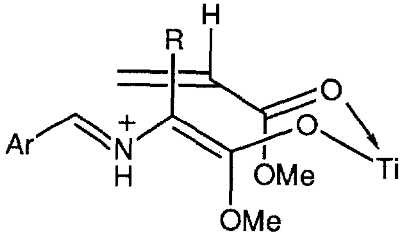


(2)



(3)

a. R = H, Ar = 2 - naphthyl
b. R = Ar = Ph
c. R = Me, Ar = Ph



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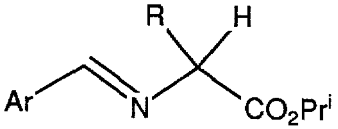
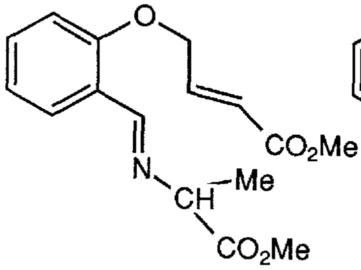
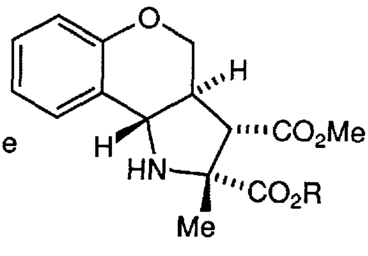


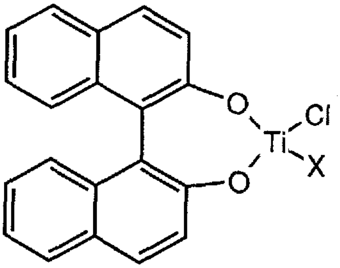
(5). a. R = H, Ar = 2-naphthyl
b. R = Ar = Ph
c. R = Me, Ar = Ph



(6)



(7) a. R = Me
b. R = Pr^i



(8) a. X = OPr^i
b. X = Cl

of cycloadducts (2a) and (3a). The regio- and stereo-chemistry of the cycloadducts was established by ^{1}H n.m.r. studies including n.O.e. data. Analogous results were obtained with (1b), which gave a 1.2 : 1 mixture of (2b) and (3b), and with (1c) which afforded a1 : 1 mixture of (2c) and (3c) (dry CH_2Cl_2 used as solvent). Combined yields of the (2a-c) and (3a-c) ranged from 69-89%. The regiochemistry of the cycloadducts (2) and (3) is the opposite to that usually obtained,[2] and implicates an intermediate, such as (4), in which both the imine and the dipolarophile ester groups are coordinated to Ti(IV).

The regiospecific transesterification that is required to produce (3) could occur in the imine (1) or the pyrrolidine (2). Appropriate experiments demonstrated that the former was the case. Transesterification of (1a-c) to give (5a-c) occurs in dry THF or dry methylene chloride at room temperature in the presence of $Ti(OPr^i)_3Cl$ (1.5 mol). Yields of transesterified imine (5) are essentially quantitative but are reduced to 55-97% upon isolation due to varying amounts of imine hydrolysis to the corresponding amine and aldehyde. $Ti(OR)_4$ has been reported to effect transesterification but under more vigorous conditions.[7] The transesterified pyrrolidines (3a-c) can be obtained as the sole products by reacting (1a-c) (1 mol) with $Ti(OPr^i)_3Cl$ (1.5 mol) for 5 h at room temperature followed by addition of methyl acrylate (2 mol) and triethylamine (1 mol). The methyl ester (2) does not transesterify to (3) on treatment with $Ti(OPr^i)_3Cl$ in dry THF or dry methylene chloride at room temperature.

The titanium (IV) complex $Ti(OPr^i)_2Cl_2$ also promotes the same cycloaddition reactions in dry methylene chloride at room temperature. Thus (1b) and methyl acrylate gave (70%) a 4.8 : 1 mixture of (2b) and (3b), whilst (1c) afforded (74%) a 1.7 : 1 mixture of (2c) and (3c). Intromolecular cycloaddition can also be achieved with both the Ti(IV) catalysts in methylene chloride. Thus (6) gives mainly (7a) together with ~10% of (7b) in *ca.* 65% combined yield.

Attempts to achieve asymmetric induction in the cycloaddition reactions of imines (1a) and (1b) with methyl acrylate using the chiral titanium (IV) complexes (8a) and (8b) were unsuccessful. These chiral complexes failed to promote the cycloaddition reactions. Further work with other imines[8] and dipolarophiles is in hand.

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