Tandem Michael Addition–1,3-Dipolar Cycloaddition of Imines of α-Amino Acid Esters and Aminoacetonitrile

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Four classes of new tandem Michael addition–1,3-dipolar cyclo-addition processes of imines of

Imine (3a) reacts with phenyl vinyl sulphone (MeCN, LiBr–NEt$_3$, 2.5 h) to give a 2:1:1 mixture (60%) of (9a), (10a), and (11a). The same reaction using silver acetate–triethylamine in DMSO (25 °C, 20 min) gives a 10:1 mixture (72%) of (10a) and (11a) whilst in acetonitrile (25 °C, 2.5 h) the products consisted of a 3:1 mixture (81%) of (10a) and (11a). In neither of these cases was any Michael adduct detected. Moreover (9a) failed to cyclise when treated with either silver acetate–triethylamine (DMSO) or lithium bromide–triethylamine (MeCN) over 48 h and (11a) did not epimerise to (10a) under these conditions. Imine (12) reacts (MeCN, 25 °C, 5 h) with phenyl vinyl sulphone in the presence of lithium bromide–triethylamine to give Michael adduct (9b) (50%) together with imine hydrolysis products. The same reaction in the presence of silver acetate–triethylamine (DMSO, 25 °C, 5 h) gives a 10:3 mixture (72%) of cycloadducts [(10b), (11b)] and Michael adduct (9b).
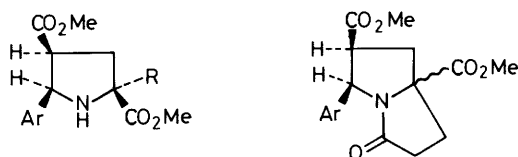
(13) a, Ar = 2-naphthyl, R = H   (14) Ar = 2-naphthyl
　　 b, Ar = 2-naphthyl
　　 R = (CH$_2$)$_2$CO$_2$Me

The tendency of lithium bromide–triethylamine in acetonitrile to produce Michael adduct is again apparent in the reaction of (3a) with methyl acrylate (LiBr–NEt$_3$, MeCN, 25 °C, 0.5 h) which gives a 1:1 mixture (71%) of cycloadduct (13a) and (14).[3] Lactam (14) would appear to arise via the Michael adduct (9c). Indeed, when Michael adduct (9c)[1] was subjected to the same reaction conditions with methyl acrylate (1 mol) it afforded a 3:1 mixture of (14) and (13b) together with a third product tentatively identified as (9d). Appropriate blank experiments show (13b) is not a precursor of (14). The reaction (MeCN, 25 °C, 0.5 h) of (3a) and methyl acrylate in the presence of silver acetate–triethylamine gives only cycloadduct (13a).[3] Chiral silver salts such as the disilver salts of L-tartaric acid and di(O-benzoyl)-L-tartaric acid also effect the cycloaddition (3a) ——→ (13a) but give products devoid of optical activity.

The lithium bromide catalysed reactions are, in general, noticeably slower than the silver acetate catalysed processes and Michael addition competes more effectively with cycloaddition in the former case. The carbanion character of the lithiated intermediate dominates with imine (12). The tendency of the small 'hard' lithium cation to complex with oxygen donor groups and of the 'soft' silver(I) cation to complex with nitrogen donor groups, in conjunction with the substrate structure, forms the basis for the differences observed. Thus the poor yield obtained from the reaction of (3c) and (4) under the influence of LiBr–NEt$_3$ is due to the lack of an oxygen donor group in (3c).

We recently disclosed powerful new C–C bond forming methodology involving tandem Michael addition–cycloaddition processes in oximes.[5] The initial Michael addition reaction in the oxime process involves the lone pair on the central atom (Y=N) of the Y=Y–ZH system, whilst the initial Michael addition in the imine process described herein involves the terminal atom (Z=C). Both processes can be similarly analysed in terms of four classes (Table). The formation of (14) constitutes an example of a class 1 process whilst formation of

Table. Synthetic variants of the tandem Michael addition–1,3-dipolar cycloaddition processes

Class	Michael addition	1,3-Dipolar cycloaddition
1	Intermolecular	Intermolecular
2	Intermolecular	Intramolecular
3	Intramolecular	Intermolecular
4	Intramolecular	Intramolecular

(5a—d) and (7) represent examples of class 2. Examples of classes 3 and 4 remain to be developed.

Experimental

General Procedure for Tandem Michael Addition–Cycloaddition of Imines to Divinyl Sulphone.—Imine (3a—d) (1 mol), lithium bromide (1.5 mol), and divinyl sulphone (1 mol) were dissolved in dry acetonitrile and triethylamine (1 mol) was added dropwise over ca. 5 min. The resulting solution was stirred at room temperature for the time noted in the text and then diluted with chloroform and washed with saturated ammonium chloride solution. The dried chloroform extract was evaporated and the product crystallised from an appropriate solvent. Compound (5a) colourless plates from ether, m.p. 96—98 °C (Found: C, 62.80; H, 5.75; N, 4.00. C$_{18}$H$_{19}$NO$_4$S requires C, 62.60; H, 5.55; N, 4.05%); m/z(%) 345 (M^+, 20), 286(30), 281(92), 266(37), 222(100), 193(72), and 169(57); δ_H(CDCl$_3$) 7.79 and 7.45 (4 H and 3 H, 2 × m, ArH), 4.60 (1 H, dd, J 5.8 and 10.3 Hz, ArCH), 3.84 (1 H, d, CHSO$_2$), 3.82 (3 H, s, OMe), 3.33 (2 H, m, CH$_2$SO$_2$), 2.90 and 2.68 (2 × 1 H, 2 × m, ArCHCH$_2$), and 2.25 (2 H, m, CH$_2$CH$_2$SO$_2$).

Note added in proof. S. Kanemasa, M. Yoshioka, and O. Tsuge, *Bull. Chem. Soc. Jpn.*, 1989, **62**, 869 have reported competing Michael addition and 1,3-dipolar cycloaddition processes for the reaction of imine (12) with methyl acrylate in tetrahydrofuran in the presence of LiBr–NEt$_3$

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