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Tandem 1,3-Azaprotio Cyclotransfer-Cycloaddition Reactions Between Ketoximes and Divinyl Ketone or its Equivalents: Lewis Acid Mediated Rate Enhancement and Control of Cycloaddition Regioselectivity

Imaad S. Saba,[a] Martyn Frederickson,[a] Ronald Grigg,[a]* Peter J. Dunn,[b] and Philip C. Levett[b]

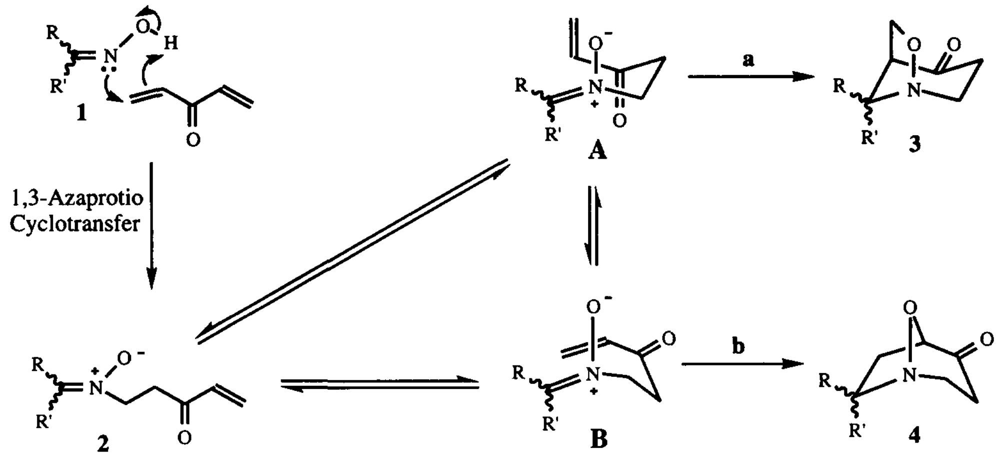
a. School of Chemistry, The University of Leeds, Leeds, U.K., LS2 9JT.
b. Pfizer Central Research (U.K.), Sandwich, Kent, U.K., CT13 9NJ.

Abstract: The tandem 1,3-azaprotio cyclotransfer-cycloaddition reaction between a ketoxime and divinyl ketone or its equivalents [2-chloroethyl vinyl ketone and bis(2-chloroethyl) ketone] affords high yields of substituted 1-aza-7-oxabicyclo[3.2.1]octan-4-ones and 1-aza-8-oxabicylo[3.2.1]octan-4-ones. Addition of zinc bromide results both in rate enhancement and control of cycloaddition regioselectivity affording almost exclusively 1-aza-7-oxabicyclo[3.2.1]octan-4-ones. © 1997 Elsevier Science Ltd.

As part of our continuing interest in the use of cascade cycloaddition reactions of oximes we recently outlined our efforts to prepare enantiopure bicyclic isoxazolidines[1,2] *via* our tandem 1,3-azaprotio cyclotransfer-cycloaddition route.[3] We showed that the reaction between divinyl sulphone and a chiral aldoxime containing one or more stereocentres (bearing hydrogen, carbon and oxygen functionalities) proceeds with complete regiochemical control and with a high level of π-facial selectivity in the terminating cycloaddition step to afford enantiopure bicyclic isoxazolidines containing three newly formed contiguous stereogenic centres, selectivity being greatest (d.e. >90%) when the nearest stereocentre is located α to the oxime moiety and is conformationally constrained as part of a ring system.[1,2]

We have been similarly interested in the use of ketonic equivalents of divinyl sulphone in these Class 2 cascades[4] because of the greater synthetic possibilities associated with the incorporation of ketonic functionality into the bicyclic isoxazolidine products which might then be viewed as useful precursors *en route* to various alkaloids and other related natural products; accordingly we have investigated the use of divinyl ketone,[5] 2-chloroethyl vinyl ketone[6] and bis(2-chloroethyl) ketone[7] as bifunctional azaprotiophile /dipolarophile species.

The reaction between an achiral ketoxime **1** and divinyl ketone (or its equivalents) may in principle occur *via* a number of differing pathways including the synthetically less useful *O*-Michael addition; in all cases polymerization of divinyl ketone is also a potential problem. The desired 1,3-azaprotio cyclotransfer process (*Scheme*) leads (in non-symmetrical cases) to a pair of possible nitrone intermediates **2**. Subsequent cycloaddition can occur *via* either of two possible pre-transition state conformations (**A** and **B**) of the latter, in opposite regiochemical senses, *via* pathways **a** and **b** giving rise to four possible diastereomeric products **3** and **4**. Chiral ketoximes (chirality in either R or R') allow the formation of a further four possible diastereoisomers since each possible cycloaddition process may occur at either of the two diastereotopic faces of the intermediate nitrone.

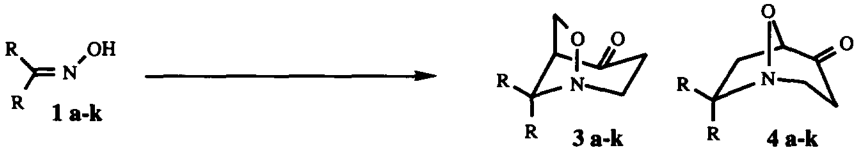


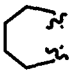
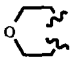
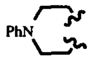
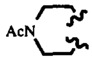
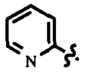
Scheme

Initial experiments involving cyclohexanone oxime **1c** and pre-formed divinyl ketone[5] showed the desired reaction to be somewhat capricious in terms of yield of products **3c** and **4c** mainly due to polymerization of the highly activated ketone although high dilution techniques (oxime:solvent 1 mmol:15 ml) reduced this problem. Thus reaction between **1c** and divinyl ketone (PhMe, 110°C, 16 h) afforded a 1:2 mixture of cycloadducts **3c** and **4c** in 72% yield.[8] Formation of divinyl ketone *in situ* either from 2-chloroethyl vinyl ketone[6] or from bis(2-chloroethyl) ketone[7] under basic conditions was studied next. Both reagents afforded high levels of reproducibility in terms of yield of cycloadducts allowing the synthesis of **3** and **4** on a larger scale without the need for high dilution, bis(2-chloroethyl) ketone ultimately proving to be the reagent of choice. Choice of base proved crucial to the success of the reaction. Use of DBU resulted in too rapid a dehydrochlorination resulting in high levels of polymerization and reduced yields whereas use of sodium carbonate resulted in extended reaction times (up to one week). Potassium carbonate proved to be an effective compromise inducing little polymerization and resulting in more acceptable reaction times. Polar solvents (acetone, tetrahydrofuran or acetonitrile or dimethyl sulphoxide) favoured cycloadducts **4** whereas apolar solvents (cyclohexane or toluene) enhanced the formation of the regioisomeric products **3** (*Table 1*). Thus, for example, cyclohexanone oxime **1c** affords the following ratios of **3c**:**4c** with variation of solvent: toluene (1:2), tetrahydrofuran (1:4), dimethyl sulphoxide 1:8).

Interest in the possibility of enhancing the rate of reaction and controlling cycloaddition regioselectivity led us to investigate the use of a range of Lewis acid catalysts ($TiCl_4$, TiO_2, $SnCl_4$, SnI_4, $MgBr_2$, ZnO, $ZnCl_2$, $ZnBr_2$, ZnI_2). Anhydrous zinc salts were found to be the most effective, particularly the bromide. Thus treatment of oximes **1b-d** with divinyl ketone (1·5 mol equiv) and anhydrous zinc bromide (1·5 mol equiv) in boiling tetrahydrofuran resulted in conversion to **3b-c** and **4b-d** in excellent yield, (*Table 2*), in all cases the 1-aza-7-oxabicyclo[3.2.1]octan-4-ones **3** were the major (or exclusive) products.

Table 1



Oxime **1**	R	Conditions [a]	Solvent [b]	**3**:**4**	Time (h)	**3** (%)	**4** (%)	Yield (%)
a		A	MeCN	1:3	20	20	54	74
b		B	Cyclohexane	5:1	48	64	14	78
c		A	THF	1:4	72	14	56	70
d		A	PhMe	1:2	16	32	51	83
e		A	PhMe	1:2	16	19	37	56
f	Me	A	Me_2CO	1:4	72	18	72	90
f	Me	B	Cyclohexane	1:1	48	41	43	84
g		A	MeCN	1:7	48	7	48	55
h		B	MeCN	1:10	48	7	70	77
i		B	MeCN	1:15	48	5	60	65
j		B	MeCN	1:7	48	9	67	76
k		A	MeCN	**4k** only	20	—	30	30

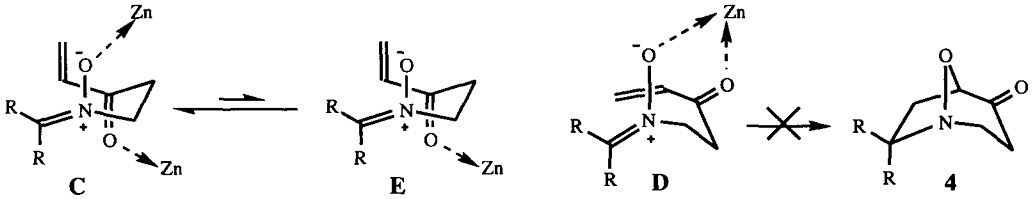
a. A: bis(2-chloroethyl)ketone (1·2 equiv), K_2CO_3 (2·0 equiv); B: divinyl ketone (1·1 equiv), degassed solvent

b. All reactions carried out in boiling solvent

Table 2

Oxime **1**	Solvent	Time (h)	**3**:**4**	Yield (%)
b	THF	6	**3b** only	95
c	THF	6	97:3	97
d	THF	16	91:9	96

The precise role of the zinc salt is a matter of conjecture.[9] Clearly the nitrone moiety is a far better ligand for Zn (II) than the carbonyl group and whilst pre-transition state conformer **B** has favourable geometry for chelation of both moieties as in **D** such chelation would be expected to suppress cycloaddition. Similar chelation in pre-transition state conformer **A** cannot occur although coordination of two Zn (II) ions is a possibility in this case as shown in **C**. A small equilibrium concentration of **E** would then lead to **3**. In this latter case, coulombic interactions between the dipole and dipolarophile moieties are enhanced. Similar Lewis acid promoted rate enhancements in intermolecular nitrone cycloadditions have been noted previously by Kanemasa's group[10-12] but their assertion that bidentate and tridentate dipolarophiles[11] are responsible for the Lewis acid catalysis is clearly not tenable in our examples.



Further work is in progress to extend these findings to enantiopure ketoximes, to study the factors affecting regioselectivity in these processes and to apply these novel cascades in the syntheses of natural products and related biologically active molecules.

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