Tetrahedron Letters, Vol.22, No.29, pp 2727 - 2730, 1981
Printed in Great Britain

0040-4039/81/292727-04$02.00/0

A CONVERGENT SYNTHESIS OF SUBSTITUTED PYRROLIDINES BY 1,3 DIPOLAR CYCLOADDITION

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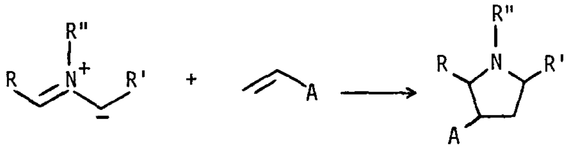
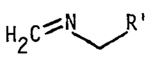
Summary: Thiazolium ylids 2a and 2b are converted to 4 in 3 steps.

The 1,3-dipolar cycloaddition of azomethine ylids with activated alkenes constitutes an effective synthetic method for certain pyrrolidines.[1] However, the reaction is rather limited in that R and R' are invariably aryl substituents or electron withdrawing groups. These restrictions stem from the synthetic methods used to generate the azomethine ylid: deprotonation of imminium salts and the thermal or photochemical openings of aziridines. Since imines for which R=H (1) are unstable and prone to trimerization,[2] the corresponding imminium salts leading to azomethine ylids have never been reported. Except for a publication of the thermolysis of 2-carboethoxy-N-phenyl aziridine,[3] no azomethine ylids with R=H have been reported. Such azomethine ylids or synthetic equivalents thereof would greatly increase the generality of the 1,3-dipolar cycloaddition. We wish to report the use of ylids 2a and 2b to afford adducts 3. These adducts can be desulfurized and hydrolyzed to form pyrrolidines 4.

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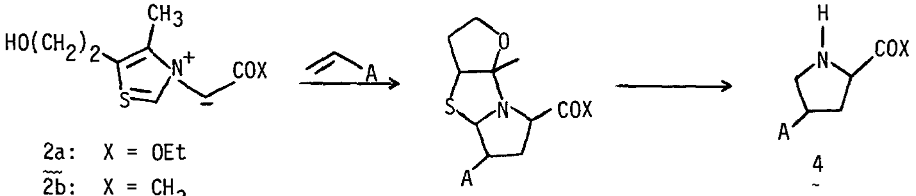


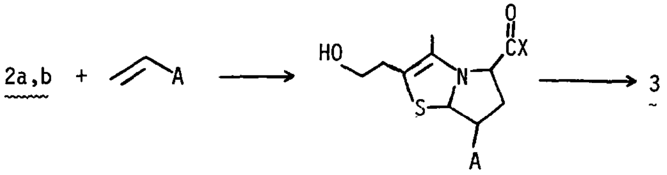
2a: X = OEt
2b: X = CH_3

3

4

A = electron withdrawing group

Ylids 2a and 2b can be conveniently prepared in excellent yields from commercially available 5-hydroxyethyl-4-methyl thiazole and ethyl bromoacetate and chloroacetone, respectively. The azomethine ylids[4] can be generated in situ at subambient temperature and cyclize in good to excellent yields with several unsaturated compounds as depicted in Table I. The initial adducts 5 cyclize upon workup to furnish 3. In some cases (entries 3 and 4) the corresponding adduct 5 can actually be isolated. However, filtration chromatography on silica gel effects cyclization to 3. The structure of 3 is supported by a singlet in a range from 1.48-1.56δ and a doublet (J = 7 Hz) in a range from 5.21-5.48δ, depending on the specific compound.



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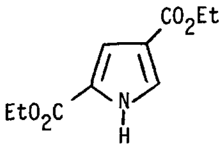
The ^{13}C NMR spectrums exhibited absorptions around 110 and 170 ppm. Inspection of Dreiding molecular models consistent with J = 7 Hz indicates that the activating group and the methine at C2 of the thiazolidine ring are trans. The product from the reaction of 2a and ethyl acrylate (entry 6) was used as a model system for the transformation to 4 (X = OEt, A = CO$_2$-Et). Reaction with Raney nickel (W4) afforded a complicated mixture of products. This was not unexpected in view of conflicting literature reports.[5] Reaction with methanesulfonic acid in methanol followed by quenching with excess triethylamine produced a good yield of 6. Presumably this resulted from oxidation of 7.[8] Compound 6 was identical to an authentic sample prepared by Rapoport and coworkers.[6] The reaction with aqueous silver nitrate (pH7-8)[7] afforded 7(δ3.08(brd,J=8Hz,2H),4.48(m,1H),7.39(m,3H)) in 94% yield. Reduction with methanolic sodium borohydride furnished 4 (X = OEt, A = CO$_2$Et) in 85% yield.



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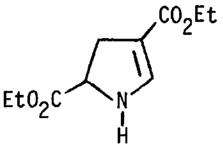

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The three step transformation to 4 clearly represents a convenient entry to this class of compounds. It extends the utility of the 1,3-dipolar cycloaddition to simpler pyrrolidines. We are currently investigating the application of this chemistry to the synthesis of allokainic acid.

Table I - Dipolar Cycloadditions

Entry	Ylid	Dipolarophile	Conditions[a]	% yield of 3[b,d]
1	**2b**	$CH_3CHCHCOCH_3$	R.T., 6h	65.1
2	**2b**	H_2CCHCO_2Et	0°, 2h; R.T., 2h	97.7
3	**2b**	*trans*·$CH_3O_2CCHCHCO_2CH_3$	0°, 2h; R.T., 2h	88.9
4	**2b**	*cis*·$CH_3O_2CCHCHCO_2CH_3$	0°, 3h; R.T., 3h	89.5
5	**2a**	$CH_3CHCHCOCH_3$	0°, 2h, R.T., 3h	70.0
6	**2a**	H_2CCHCO_2Et	0°, 2h, R.T., 3h	72.6
7	**2b**	H_2CCHCN	0°, 2h	57.5
8	**2b**	PhCHCHCHO	0°, 2h	--[c]
9	**2b**	$CH_3CHCHCHCHCO_2CH_3$	0°, 3h; R.T., 2h	61.0

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[a] Unsaturated carbonyl compound, **2a** or **2b** were suspended in CH_3CN at 0° C. Triethyl amine was added dropwise and the suspension was stirred at temperatures indicated above. The reaction was diluted with ether and water and worked up in a standard manner. The crude product was purified by filtration chromatography.

[b] Structures supported by ^1H and ^{13}C NMR, IR and high resolution mass spectroscopy or elemental analysis.

[c] Upon addition of base, an immediate black suspension developed. No recognizable products were isolated.

[d] Representative spectra: Entry 6: δ 1.24(t, J = 7 Hz, 3H), 1.49(s, 3H), 1.9-2.8 (m, 4H), 4.15(q, J = 7 Hz, 2H), 5.2(d, J = 7 Hz). CMR($CDCl_3$): 172.7, 170.2, 109.8, 75.0, 65.87, 60.8, 60.6, 55.1, 46.3, 33.6, 29.2, 22.2, 13.8. IR(film): 1735(br) cm^{-1}. Entry 1: δ 0.95(d, J = 7 Hz, 3H), 1.51(s, 3H), 2.20(s, 3H), 2.23(s, 3H), 2.9-3.35(m, 1H), 3.75-4.2(m, 2H), 5.31(d, J = 7 Hz, 1H). IR(film): 1710, 1715 cm^{-1}. CMR($CDCl_3$): 210.9, 203.1, 109.9, 75.6, 74.8, 72.2, 66.3, 61.8, 56.7, 33.94, 29.7, 28.8, 22.5, 14.3.

Acknowledgement - We thank the Alfred P. Sloan Foundation for support of this work.

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8. A referee noted that 6 might have arisen directly by two elimination reactions. This is possible. However, no pyrrole was formed when the reactant was treated with excess base.

(Received in USA 12 March 1981)