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CYCLOAROMATIZATION OF α-OXOKETENE DITHIOACETALS WITH 3-METHYL-5-LITHIOMETHYLISOXAZOLE: A NEW GENERAL APPROACH FOR SYNTHESIS OF SUBSTITUTED AND ANNELATED 1,2-BENZISOXAZOLES[1]

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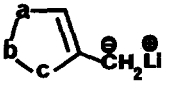
Summary: A new general method for the synthesis of substituted and annelated 1,2-benzisoxazoles has been developed by cycloaromatization of α-oxoketene dithioacetals with 3-methyl-5-lithiomethylisoxazole.

The discovery of our aromatic (or heteroaromatic) annelation involving the reaction of allyl[2], benzyl[3], propargyl[4] magnesium halides, 2-picolyllithium[5] and Reformatsky reagent[1] with α-oxoketene dithioacetals has been shown to be of general application to yield the corresponding substituted benzene, naphthalene, polycyclic aromatic and quinolizinium compounds in good yields. The overall process was aimed at creating the aromatic ring systems from easily available aliphatic precursors. In continuation of these studies, we propose yet another broad based plan to explore the possibilities of annelating aromatic ring over preconstructed five membered heterocycles by condensing α-oxoketene dithioacetals with lithioallyl systems of general formula 1. As a part of this programme, we have studied the reaction of 3-methyl-5-lithiomethylisoxazole (3) with α-oxoketene dithioacetals 2 to yield the corresponding substituted and annelated 1,2-benzisoxazoles 6 in good yields. We herein report our results in this communication.



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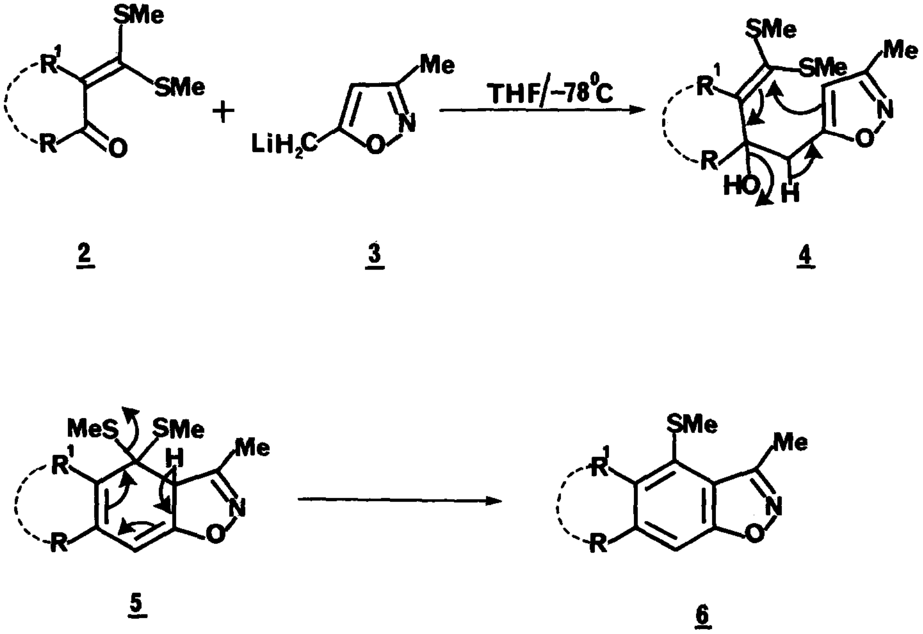
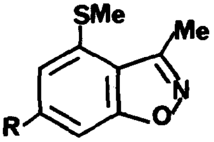
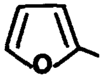
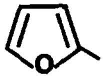
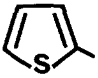
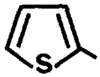
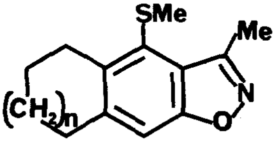
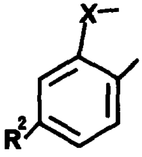
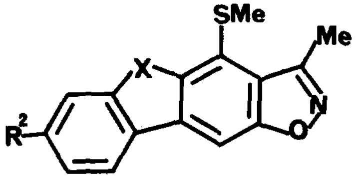
When 2a was reacted with 3 at -78°C, the corresponding carbinol acetal 4a was obtained in nearly quantitative yield, which was directly subjected to cyclization in the presence of boron trifluoride etherate in refluxing benzene to give a colourless crystalline product, characterized as 3-methyl-4-methylthio-6-phenyl-1,2-benzisoxazole (6a) (73%); ν_{max}(KBr): 1600, 1566, 1425, 1388, 1345 cm^{-1}; ^{1}H n.m.r. (CCl_4) (90 MHz): δ 2.56(s,3H,C$\underline{H}_3$); 2.68(s,3H, SC$\underline{H}_3$); 7.02(brs,1H,$\underline{H}$-7), 7.20-7.67(m,6H,ArH), δ_C ($CDCl_3$); 11.47($\underline{C}H_3$); 17.23(S$\underline{C}H_3$); 103.80, 114.59(C-7 and C-5); 125.45, 127.24, 128.35, (CH, phenyl); 128.36, 140.20, 142.66, 142.41 (quaternary C); 159.71 (C-3); 168.07 (C-8); MS(m/z); 155(M^+,100%). Cycloaromatization of other acyclic dithioacetals 2b-g with 3 under identical conditions similarly afforded the corresponding 6-substituted 1,2-benzisoxazoles 6b-g in 54-68% overall yields[6]. The corresponding 5,6-annelated 1,2-benzisoxazole 6h-l were similarly obtained from the respective cyclic dithioacetals 2h-l in 57-81% yields[6].

The overall transformation is shown in the Scheme. The carbinols 4 undergo cyclodehydration as expected by participation of the isoxazole 4,5 double bond, followed by elimination of methylmercapto group to give the desired benzisoxazoles 6 in good yields. The reported methods for 1,2-benzisoxazoles apparently involve construction of isoxazole ring on either functionalized benzene ring or cyclohexane derivatives[7a]. The present reaction, utilizing easily accessible α-oxoketene dithioacetals from a variety of acyclic and cyclic active methylene ketones, provides a novel approach for substituted and annelated 1,2-benzisoxazoles through benzoannelation of isoxazole derivative. Further work to extend this method for the synthesis of other benzoheterocycles is in progress.



Scheme

Table

Entry	Starting material	R	R^1	Product	Yield[a] %	m.p. °C
						
1	2a	C_6H_5	H	6a, R = C_6H_5	73	70
2	2b	4-Cl C_6H_4	H	6b, R = 4-ClC_6H_4	66	155
3	2c	4-MeOC_6H_4	H	6c, R = 4-MeOC_6H_4	68	130
4	2d	β-naphthyl	H	6d, R = β-naphthyl	64	145
5	2e	Me	H	6e, R = Me	54	85
6	2f		H	6f, R = 	59	110
7	2g		H	6g, R = 	61	125
						
8	2h	$-(CH_2)_4-$		6h, n = 1	65	42
9	2i	$-(CH_2)_5-$		6i, n = 2	67	62
						
10	2j	R^2=H, X = $-CH_2-$		6j, R^2=H, X = $-CH_2-$	57	160
11	2k	R^2=H, X = $-(CH_2)_2-$		6k, R^2=H, X = $-(CH_2)_2-$	76	152
12	2l	R^2=CH_3, X = $-S-(CH_2)_2-$		6l, R^2=CH_3, X = $-S-(CH_2)_2-$	81	185

[a] Yield of pure isolated product based on 2

In a typical experiment, a solution of 2a (2.24g, 0.01 mol) in THF (25 ml) is added to a solution of 3-methyl-5-lithiomethylisoxazole[7b,8] (0.015 mol in 25 ml of THF) at -78°C under N_2 atmosphere and the reaction mixture is further stirred at the same temperature for 0.5 hr. It is then warmed to 0°C (1 hr) and stirring is continued further for 2 hr. Work-up of the reaction mixture as described earlier[3] gave the crude carbinol 4a (3.05g, 95%) as viscous liquid, which was dissolved in dry benzene (50ml)treated with boron trifluoride etherate(2 ml) refluxed for 1 hr. The reaction mixture was then poured over cold saturated $NaHCO_3$ solution, extracted with $CHCl_3$(2x50 ml), washed with water, dried (Na_2SO_4) and evaporated to give a viscous residue, which was purified by passing through silica gel column (hexane as eluent) to give 6a as colourless crystals (chloroform), 1.86g (73%).

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References and Notes

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6. All the product benzisoxazoles 6b-l were characterized with the help of spectral and analytical data; selected data for:

   6h: ν_{max} (KBr): 1605, 1580, 1430, 1380, 1330, 1300 cm^{-1}; δ_H (CCl_4): 1.61-1.98(m,4H,$C\underline{H}_2$); 2.34(s,3H,$C\underline{H}_3$); 2.66(s,3H,$SC\underline{H}_3$); 2.60-3.13(m,4H,$C\underline{H}_2$); 7.01(s,1H,Ar$\underline{H}$); m/z:233(M^+,93%).

   6k: ν_{max} (KBr): 1600, 1585, 1513, 1430, 1386, 1345, 1250 cm^{-1}; δ_H ($CDCl_3$): 2.30(s,3H, $C\underline{H}_3$); 2.80(s,3H,$SC\underline{H}_3$); 2.72-3.43(m,A_2B_2,4H,$C\underline{H}_2$); 7.16-7.38(m,3H,Ar$\underline{H}$); 7.60-7.83(m,2H,Ar$\underline{H}$); δ_C($CDCl_3$): 12.75($\underline{C}H_3$); 20.14($S\underline{C}H_3$); 26.04($\underline{C}H_2$); 29.16($\underline{C}H_2$); 105.61, 124.88, 127.24, 127.97, 128.60($\underline{C}H$, aromatic); 123.03, 128.91, 134.24, 134.26, 138.17, 138.26, 155.83, 162.50(quaternary $\underline{C}$); m/z:281(M^+,100%).
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