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# Synthesis and Lewis Acid Assisted Rearrangement of Novel Donor-Acceptor Substituted Cyclopropanes: Highly Stereoselective [4+1] Annulation Approach to Substituted and Spiro Cyclopentene Derivatives

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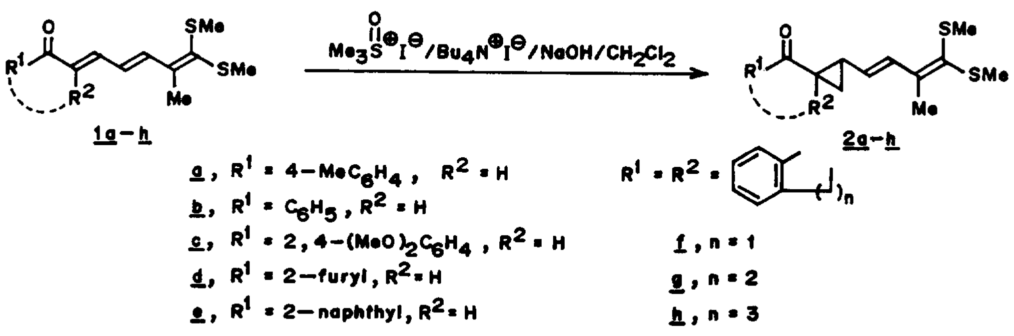
*Abstract*: The cyclopropanes **2a-h** having 4-(bismethylthio)butadienyl moiety as donor group, which are easily obtained by regioselective cyclopropanation of vinylogous ketene dithioacetals **1a-h** with oxodimethylsulphonium methylide, undergo facile Lewis acid assisted vinylcyclopropyl rearrangement to afford substituted and spiro cyclopentenes **3a-h** in good yields.

The development of newer synthetic strategies for the construction of five membered ring has been very active area of research in recent years.[1] Particularly impressive are a number of approaches involving cyclopropane ring expansion reactions.[2] A major contribution to this area has been Hudlicky's [4+1][3] annulation approach based on cyclopropanation of dienes and subsequent 1,3-sigmatropic rearrangement of the resulting vinylcyclopropanes to cyclopentene derivatives. A number of vinylcyclopropanes with a variety of substitution pattern have been prepared and their reactivity studied.[4] In particular, the vinylcyclopropanes containing both donor and acceptor functionalities were found to be very effective, because of their facile ring expansion under milder conditions through zwitterionic intermediate.[5] Several methods are available for the synthesis of donor acceptor substituted cyclopropanes, but the most general approach has been cyclopropanation of electron rich dienes by metal stabilized carbenes.[5b,6a] Harsh thermal conditions were originaly required for ring expansion of vinylcyclopropanes, since then, a number of milder procedures using catalysts such as $(C_2H_4)_2Rh(acac)$[7] and $Et_2AlCl$[6-7] have been reported. We have recently described in a series of papers, a new synthesis of substituted cyclopentane derivatives through cationic rearrangement of substituted bis(methylthio)methylenecyclopropyl ketones.[8] During the course of these studies, we have synthesized novel donor acceptor substituted cyclopropanes through cyclopropanation of vinylogous oxoketene dithioacetals **1** with oxodimethylsulphonium methylide and studied their rearrangement in the presence of Lewis acid to afford functionalized cyclopentenes and the corresponding spiro derivatives in highly regio- and stereoselective manner. We report the results of our preliminary studies in this communication.

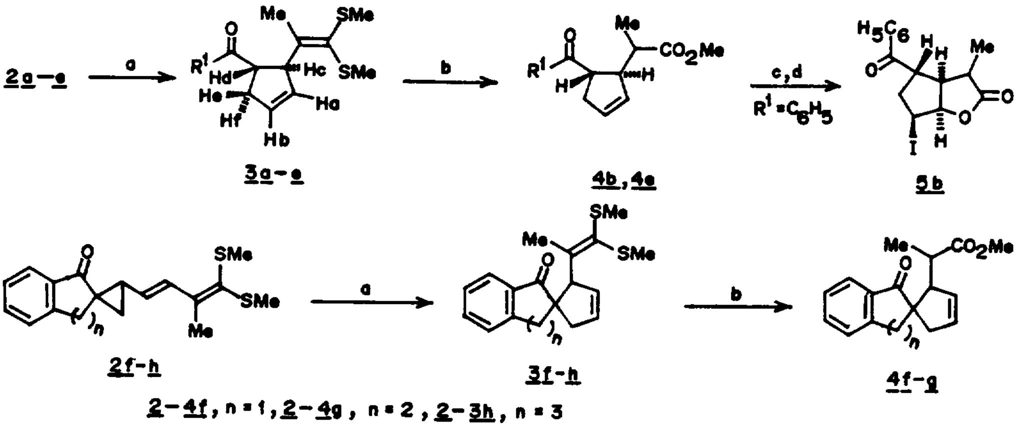
The desired vinylogous ketene dithioacetals **1a-h** were synthesized according to our earlier reported procedure by base catalyzed condensation of respective active methylene ketones with 5-bis(methylthio)-4-methyl-2,4-pentadienal.[9] These trienones **1a-h** underwent highly regio and stereoselective cyclopropanation with oxodimethylsulphonium methylide (generated in the presence of phase transfer



Scheme – 1

catalyst)[8] to afford the novel 1-aroyl (or 1,1-spiro) cyclopropanes **2a-h**[10,11] in high yields[8] (Scheme 1). Lewis acid induced rearrangement of these newly synthesized dienylcyclopropyl ketones was next investigated. In a typical experiment, **2a** was stirred with stannic chloride in nitromethane at 0°C for 3hr (monitored by TLC); subsequent work-up of the reaction mixture afforded only one product (63%) characterized as cyclopentene **3a**[11] on the basis of spectral and analytical data. The other substituted 1-aroylcyclopentenes **3b-e**[11] were similarly obtained in 61-69% overall yields under identical conditions.[12] The cyclopentenes **3b** and **3e** were subjected to $BF_3.Et_2O$ assisted methanolysis for converting ketene dithioacetal moiety into carbomethoxy group to afford the corresponding esters **4b** and **4e** respectively in nearly quantitative yields.

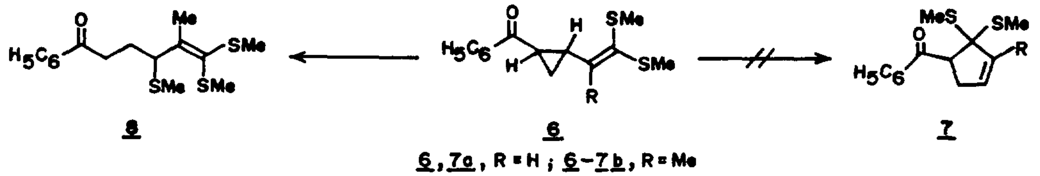
The versatility of this transformation was further evident when the spirocyclopropyl ketones **2f-h** underwent facile rearrangement in the presence of $SnCl_4/CH_3NO_2$ to afford the corresponding spiro cyclopentenes **3f-h**[11] exclusively in excellent yields (61-85%)(Scheme 2).[12] Methanolysis of **3f-g** in the presence of $BF_3.Et_2O/HgCl_2$ under identical conditions afforded the corresponding esters **4f-g**[11] in nearly quantitative yield.To further prove the scope of this reaction,one of the cyclopentene carboxylate **4b** was subjected to iodolactonization through its hydrolyzed acid to afford the corresponding bicyclic iodolactone **5b** in 65% yield. Interestingly, the bis(methylthio) vinylcyclopropane **6** failed to cyclize to the



a: $SnCl_4/CH_3NO_2$; b: $BF_3.Et_2O/HgCl_2/MeOH$; c: NaOH/MeOH/90 °C /4hr; d: $I_2/KI/H_2O/NaHCO_3$/48hr.

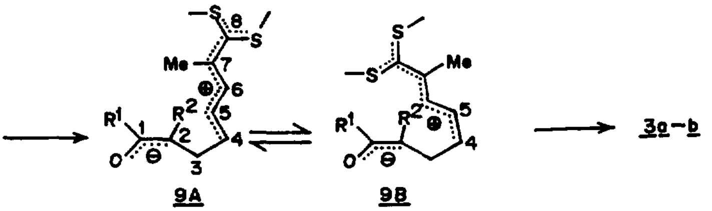
Scheme-2

corresponding **7** in the presence of $SnCl_4/CH_3NO_2$ or other Lewis acids.The only characterizable product obtained from the reaction mixture was found to be the acyclic tris(methylthio)ketone **8** (14%).



Scheme – 3

The probable mechanism for the rearrangement of **2** to **3** is shown in the Scheme 4. Lewis acid assisted cleavage of cyclopropane ring of **2** affords zwitterionic intermediate **9** equilibriating between **9A** (4,5-*E* ) or **9B** (4,5-*Z* ) orientations. The zwitterion **9B** having correct orientation cyclizes to give *trans* cyclopentenes **3** stereoselectively.



Scheme –4

In summary, we have developed an efficient highly steroselective two step [4+1] annulation approach for synthesis of substituted and spiro cyclopentenes with the feasibility of Lewis acid assisted vinylcyclopropane rearrangement. To date only a few reports of successful Lewis acid catalyzed vinylcylcopropane rearrangements have been described.[6,7] Conventional thermal vinylcyclopropane rearrangements lack regio and stereochemical control due to high temperature required for the key thermolysis step and are intervened by the side reactions such as homo [1,5] sigmatropic migration.[3c] The vinylcyclopropanes used in this study are unusual in that they contain electron donating substituents (bismethylthio group) not directly attached to cyclopropane ring but through conjugated butadienyl moiety which provides further stabilization to dipolar intermediate **9** thus significantly reducing the activation energy of vinylcyclopropane rearrangement. Further the bis(methylthio)methylene double bond in these cyclopropanes acts both as cationic cyclization terminator [13] as well as masked ester group for the synthesis of functionalized cyclopentene ring. Further studies are in progress to demonstrate scope of the reaction and to clarify the mechanism and observed stereoselectivity of this rearrangement.

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9. Since 4-unsubstituted 5-bis(methylthio)-2,4-pentadienals were found to be unstable, the corresponding 4-methyl analogs were selected for this transformation; Also see Chandrasekaram,M.; Asokan, C.V.; Ila, H.; Junjappa, H. *Tetrahedron Lett*. **1990**, *31*, 1763-1766.
10. *Data for **2a***: viscous liquid(83%); IR($CCl_4$)1667,1599,1538,1428 cm$^{-1}$; $^1$H NMR(90MHz,$CCl_4$) δ1.03-1.86(m,2H,$CH_2$),2.10(s,3H,$CH_3$),2.23(s,3H,$SCH_3$),2.30 (s,3H,$SCH_3$),2.42 (s,3H,$CH_3$),2.43-2.80 (m,2H,$CH_2$), 5.48 (dd,1H,J=17,8Hz, =C*H*),7.25 (d,2H, J=8 Hz, ArC*H*), 7.32 (d,1H, J=17Hz, =C*H*), 7.95 (d,2H, J=8Hz,Ar*H*); m/z: 318(M$^+$,100 %)
11. All the new compounds were characterized with the help of spectral and analytical data.
*Data for **3a***: viscous liquid(63%);IR($CCl_4$)1674,1599cm$^{-1}$; $^1$HNMR(250MHz,$CCl_4$)δ1.90 (s,3H,$SCH_3$), 1.98(s,3H,$SCH_3$),2.20(s,3H,$CH_3$),2.39(s,3H,$CH_3$),2.53-2.68(ddq,1H,J=16.5,9.5,2Hz,$H_e$),2.77-2.91(ddq,1H,J=16.5,5.5,1.9Hz, $H_f$),3.74(dt,1H,J=9.5,5.5Hz,$H_d$),4.90(dquint,1H,J=5.5,2Hz, $H_c$), 5.33(dq,1H, J=6,2Hz, $H_a$),5.77(dq,1H, J=6,2Hz, $H_b$),7.14(d,2H, J=9Hz,Ar*H*),7.68(d,2H, J=9Hz, Ar*H*); $^{13}$C NMR(250MHz,$CDCl_3$)16.63,17.30,17.77,21.53(2S$CH_3$,2 $CH_3$);36.47($CH_2$);48.67(*C* H), 56.11(*C* H),129.38(Ar *C*H),130.62,131.39(H*C*=),129.52,134.21(quaternary Ar *C*),143.58,145.54 (quaternary C=*C*),200.49 (*C*=O). m/z: 318 (M$^+$, 8.4%), 303 (86%),271 (93%), 223 (12%).
***3f*** :viscous liquid(64%); IR($CCl_4$) 1699,1603 cm$^{-1}$; $^1$HNMR(250MHz,$CDCl_3$) δ1.89(s,3H,$SCH_3$), 1.93(s,3H,$SCH_3$),2.18(s,3H,$CH_3$),2.51(dq,1H,J=12.13,2Hz,*H*),2.84(dq,1H,J=12.13,2Hz,*H*)2.86 (d,2H,J=12.13Hz,$CH_2$),4.83(quint,1H,J=1.8Hz,C*H*),5.63(dq,1H,J=5.8,1.8Hz, =C*H*),5.91(dq,1H, J=5.8,1.8Hz, =C*H*),7.34-7.38(m,2H,Ar*H*),7.38-7.52(m,1H, Ar*H*),7.77-7.80(m,1H,Ar*H*).
***5b***: Colourless solid (76%);mp.118-119°C;IR($CCl_4$)1763,1671 cm$^{-1}$; $^1$H NMR(250 MHz,$CDCl_3$) δ1.09 (d,3H,J=7Hz,$CH_3$),2.29(dt,1H,J=14,7Hz, *H*),2.95(quint,1H,J=6.5Hz, *H*),3.06(dq,1H,J=14,7Hz, *H*),3.68(q,1H,J=6.4Hz, *H*),3.99(dt,1H,J=7.5,6.4Hz, *H*),4.35(td,1H,J=7,2.5Hz, *H*),5.14(dd,1H, J=5.6,2.5Hz,*H*), 7.44-7.52(m,2H,Ar*H*),7.56-7.58(m,1H,Ar*H*); $^{13}$C NMR (250MHz,$CDCl_3$) 10.49 ($CH_3$), 27.11($CH_2$),32.73,34.05,35.73(*C* H),79.96(*C* HI),85.04(H *C* O), 117.43, 117.74, 122.42 (Ar *C* H), 124.38(Ar *C*),165.85(O*C* =O),185.68(Ar*C* =O); m/z: 370(M$^+$,6%), 243 (M$^+$-I, 90%).
***4f***: viscous liquid (94%); IR ($CCl_4$)1731,1678 cm$^{-1}$; $^1$H NMR (90MHz,$CDCl_3$) δ0.91 (d,3H, J=6.5Hz,$CH_3$),2.15-3.53(m,6H,2$CH_2$,2C*H*),5.75(brs,2H, =C*H*),7.3-8.0(m,4H,Ar*H*).
12. The rearrangement of **2** was found to be highly stereoselective to afford only *trans* cyclopentenes **3a-e** exclusively. The corresponding spirocyclopentenes **3f-h** were also obtained as pure diastereomers, probably *trans* in analogy with the cyclopentenes **3a-e**. The stereochemical assignments for **3a-e** were based on coupling constants as well as distinctive NOE enhancement . The coupling constants for C*H* CO (dt,$H_d$ ,J=9.5,5.5Hz)in **3a** indicates the presence of only one *syn* proton on the adjascent carbon. For cyclopentenes, $J_{syn}$ is usually larger than $J_{anti}$ although exceptions are known:(a)Hunter,G.;Miller,J.A.,Moore,M.;Ullah,G.M. *Org. Mag. Res* **1983**,*21*,275-278. (b) Trost,B.M.;Molander,G.A. *J. Am. Chem. Soc.* **1981**, *103*,5969-5972.(c) Burgess,K. *J. Org. Chem.* **1987**,*52*, 2046-2051.(d)Partridge,J.J.;Chadha,N.K.;Uskokovic,M.R. *J. Am. Chem. Soc.* **1973**,*95*, 532-540.(e)Davies,H.M.K.;Clark,T.J.;Church,L.A. *Tetrahedron Lett*. **1989**, *30*,5057-5060. Also, a NOE enhancement was observed between *syn* protons ($H_d$ and $H_e$) (8.2%) while no enhancement was observed between *anti* protons ($H_d$ and $H_c$) in **3b**.
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