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Intramolecular Carbenoid Insertions Into Thiophene: Reactions of 1-Diazo-3-(2-Thienyl)-2-Propanone and 1-Diazo-3-(3-Thienyl)-2-Propanone.

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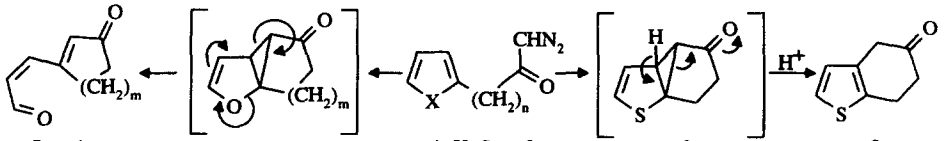
Abstract: Treatment of 1-diazo-3-(2-thienyl)-2-propanone with catalytic rhodium (II) acetate results in cyclopropanation followed by acid-catalyzed ring opening and tautomerization to yield 5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-5-one. Under the same conditions, however, the isomeric 1-diazo-3-(3-thienyl)-2-propanone generates a cyclopropane intermediate which undergoes [4+2] cycloreversion, isomerization and Diels-Alder dimerization to give a complex spiro-disulphide. While the 2-substituted thiophene behaves like other homologous members of the thienyl series, the isomeric 3-substituted thiophene undergoes chemistry seen previously with analogous furanyl compounds. The insight into the mechanistic underpinnings provided by preliminary molecular modeling at a PM3 level is discussed.

The intramolecular insertion of carbenoids into 5-membered heteroaromatics allows for access to a variety of useful ring systems in a facile and direct manner. While examples involving various heterocycles exist in chemical literature, the chemical outcome is highly dependent on the cyclization substrate.[1] Padwa, for example, has demonstrated that 1-diazo-4-(2-thienyl)-2-butanone (**1**) can be converted to 4,5,6,7-tetrahydrobenzo[*b*]thiophen-5-one (**3**) in the presence of rhodium (II) acetate.[2] The reaction proceeds *via* cyclopropanation followed by acid-catalyzed ring opening to yield an enol which tautomerizes to the ketone shown in Scheme 1. The isomeric 1-diazo-4-(3-thienyl)-2-butanone was shown to undergo similar chemistry to give a mixture of to 4,5,6,7-tetrahydrobenzo[*b*]thiophen-6-one and to 4,5,6,7-tetrahydrobenzo[*c*]thiophen-5-one. With the analogous furanyl system (**4**), however, addition of the keto carbene to the furanyl π-bond is followed by a retro-[4+2] ring opening to give keto-aldehyde **5**. Similarly, the homologous furan (**6**) was shown to cyclize to give (**7**). Pawda attributes the difference in reactivity between the thienyl and furanyl systems to the stronger C=O bond formed in the [4+2]-cycloreversion reaction carried out by the furans.



5:m=1
7:m=2

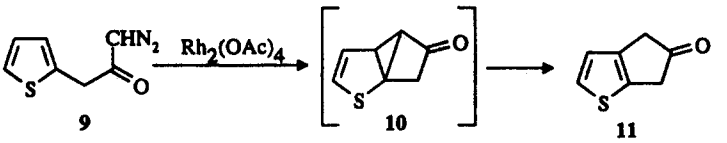
1: X=S; n=2
4: X=O; n=2
6: X=O; n=3
8: X=O; n=1

2

3

Scheme 1

As part of a planned synthesis for new antiviral agents[3], we identified 5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-5-one (**11**) as a useful synthon. While preparative routes to the compound exist[4], we envisioned a more direct route involving the intramolecular cyclization of the α-diazoketone derived from 2-thiopheneacetic acid. Treatment of 2-thiopheneacetic acid with oxalyl chloride and catalytic *N*,*N*-dimethylformamide generated 2-thiopheneacetyl chloride which was subsequently reacted with diazomethane to give 1-diazo-3-(2-thienyl)-2-propanone (**9**). Exposure of **9** to $Rh_2(OAc)_4$ in methylene chloride at 25°C for 3h afforded the desired **11** in 54% yield. Compound **11** has been characterized completely using NMR and MS.[5] Crystals of the cyclopentanone-thiophene were grown from benzene and allowed for its structure to be determined via x-ray diffraction (see Figure 1).[6] The cyclization of 1-diazo-3-(2-thienyl)-2-propanone (**9**) is very satisfying in light of the fact that the rhodium acetate catalyzed reaction of the analogous furanyl system, 1-diazo-3-(2-furanyl)-2-propanone (**8**), gives a complex mixture of products.[2] The disparate behaviour of these comparable thienyl (**9**) and furanyl (**8**) systems remains unclear.



Scheme 2

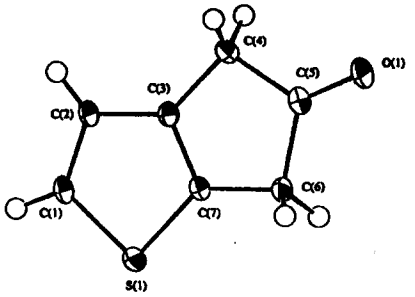


Figure 1. ORTEP view of 5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-5-one (**11**)

While **11** was likely the result of ring opening of the cyclopropane intermediate **10**, an intramolecular carbene insertion into the C-H bond at the 3-position of **9** would also give this compound. In an effort to further elucidate the mechanism of the reaction, we prepared 1-diazo-3-(3-thienyl)-2-propanone **12** and subjected it to rhodium catalyzed cyclization conditions with the expectation that, if a C-H insertion were operating, we would generate both **11** and the isomeric 5,6-dihydro-4*H*-cyclopenta[*c*]thiophen-5-one. Much to our surprise, compound **16**, whose structure has been confirmed by NMR, MS[7] and x-ray crystallography[8] (see Figure 2), was the only isolable reaction component (85% yield from the starting diazoketone).

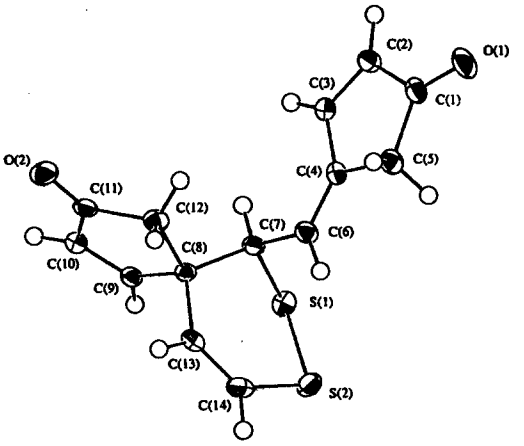
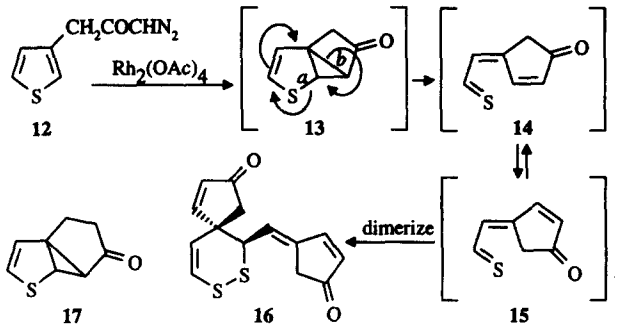


Figure 2. ORTEP view of the Spiro-disulphide (**16**)

One mechanism which would allow for this remarkable conversion is illustrated in Scheme 3. Unlike the other thiophenyl systems, opening of the initial cyclopropane intermediate (**13**) gives a thioaldehyde (**14**) *via* a [4+2]-cycloreversion seen previously only in the furanyl systems. Isomerization (to **15**) is then followed by a Diels-Alder dimerization to give **16**. The head-to-head regiochemistry of dimerization to give **16** is unusual in that head-to-tail addition would be expected based on FMO considerations. The involvement of the rhodium in this reaction is possible, but has not yet been confirmed.



Scheme 3

Other methods for carbene generation were also investigated. Decomposition of **12** in the presence of Cu metal gives a complex mixture of products while photolysis of **12** results in Arndt-Eistert type chemistry to give the homologous acid, 3-(3-thienyl)propanoic acid. These results indicate that the rhodium catalyst is essential for the transformation of **12→16** although its exact role (aside from carbenoid generation) has yet to be determined.

Why does cyclopropane **13** undergo a [4+2]-cycloreversion avoiding the acid-catalyzed enol pathway seen for the homologous thienyl diazoketones? Preliminary semi-empirical modeling studies have revealed some interesting trends. Geometry optimizations were carried out on the cyclopropanes **2**, **10**, **13** and **17** (Scheme3) and their respective [4+2]-cycloreversion products at the restricted Hartree-Fock level using the PM3 Hamiltonian in the Spartan program.[9] The thermodynamics of the reactions revealed that cycloreversion of **2**, **10**, and **17** was endothermic by 13.5, 21.3, and 12.0 kcal/mol respectively, while cycloreversion of **13** was exothermic by 10.5 kcal/mol. The relief of substantial strain energy associated with the fused tricyclic system, makes the cycloreversion of **13** thermodynamically favourable. On the other hand, similarly strained isomer **10** would be unaided by retro-[4+2] ring opening since cycloreversion leads to a highly strained cyclobutenone system. [4+2] Cycloreversion of the four analogous furan-based systems followed the same trend but were all found to be exothermic (18.8, 17.9, 46.9 and 21.5 kcal/mol for the oxy analogous of **2**, **10**, **13** and **17** respectively). As rationalized by Padwa[2], this observation is in keeping with the greater bond strength of the aldehyde C=O bond compared to the thioaldehyde C=S bond.

The transition state structures for the cycloreversion of **2**, **10**, **13** and **17** were also explored computationally. Each transition structure gave only one imaginary harmonic vibrational frequency corresponding in motion to the desired reaction co-ordinate (*ie.* stretching of bonds *a* and *b*, as in **13**). The transition state associated with the conversion **13→14** was calculated to lie 21.5 kcal/mol above the ground state energy of **13** while the energy of the transition states associated with the cycloreversions of **2**, **10**, and **17** were found to be 45.9, 43.0 and 43.7 kcal/mol above **2**, **10**, and **17** respectively. Clearly, the relief of strain in intermediate **13** facilitates cycloreversion despite the generation of a reactive C=S bond.

Mechanistic and modeling studies on these systems are continuing.

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References and Notes.

1. For examples involving furan, pyrrole and thiophene see: (a) Nwaji, M.N.; Onyiriuka, O.S., *Tetrahedron. Lett.* **1974**, 2255; (b) Wenkert, E.; Guo, Ming; Pizzo, F.; Ramachandran, K., *Helv. Chim. Acta* **1987**, *70*, 1429; (c) Wenkert, E.; Decorzant, R. and Naf, F., *Helv. Chim. Acta* **1989**, *72*, 756; (d) Padwa, A.; Wisnieff, T.J. and Walsh, E.J. *J. Org. Chem.* **1986**, *51*, 5036; (e) Jefford, C.W.; Johncock, W. *Helv.*

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2. Padwa, A.; Wisnieff; T.J.; Walsh, E.J., *J. Org. Chem.* **1989**, *54*, 299.
3. Dallemange, P.; Alsaidi, A.; Boulouard, M.; Rault, S.; Robba, M., *Heterocycles*, **1993**, *36*, 287; Dallemange, P.; Boulouard, M.; Rault, S.; Robba, M., *J. Heterocyclic Chem.*, **1993**, *30*, 799.
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5. Please see Figure 1 for atom numbering of **11**. ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 3.40 (2H, s, $C4H_2$), 3.53 (2H, s, $C6H_2$), 6.96 (1H, d, *J*=5.0 Hz, C2H), 7.24 (1H, d, J=5.0 Hz, C1H); ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ 41.74 (C4), δ 41.80 (C6), δ 122.77 (C1), δ126.60 (C2), δ 135.77 (C7), δ139.54 (C3), δ214.61 (C5); HRMS (EI+): for C_7H_6OS; calculated 138.0139, observed 138.0142.
6. For both structures **11** and **16**, unit cell determinations and data collected on a Rigaku AFC7R diffractometer with graphite-monochromated Mo-Kα radiation (λ = 0.71069 Å). The crystals were cooled with an Oxford Cryosystem Cooler (Cosier, J and Glazer A.M. *J. Appl. Crystallogr.* **1986**, *19*, 105). The structures were solved with direct methods, SHELXS-90 (Shledrick, G.M. *Acta Crystallogr. Sect. A* **1990**, *46*, 467) and refined with full-matrix least-squares refinement on F^2 with SHELXL-93 (Shledrick, G.M. SHELXL-93; Program for crystal structure refinement, Gottingen, 1993). *R*-values; $R1 = \Sigma||F_o| - |F_c|| / \Sigma|F_o|$, and $wR2 = [\Sigma w(F_o^2 - F_c^2)^2 / \Sigma w(F_o^2)^2]^{1/2}$. Further details of the crystal structure investigation can be obtained form the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Cambridge CB2 1EW, U.K. *Crystal data* for **11**: C_7H_6OS, M = 138.18, monoclinic, space group $P2_1/c$, a = 6.414(2), b = 13.309(2), c = 7.542(1) Å, β = 106.90(2)°, V = 616.0(2) Å^3, Z = 4, D_c = 1.490g cm^{-3}, $F(000)$ = 288, μ(Mo-Kα) = 0.421 mm^{-1}, T = 123 K. Intensities (h k ±l) of a colourless prism (dimensions 0.10 x 0.20 x 0.25 mm) were collected by the ω-2θ scan method to $2\theta_{max}$ = 54°. A total of 1463 reflections were collected of which 1348 were unique (R_{int} = 0.0176). Data collected for Lorentz polarization and decay (0.64%) but not for absorption. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms located by difference synthesis were included in the model but not refined. Full-matrix least-squares refinement of 82 parameters gave $R1$ = 0.0349 and $wR2$ = 0.1030 for I ≥ 2σ(I) and $R1$ = 0.0433, $wR2$ = 0.1099, S = 1.055 for all data. The largest difference peak and hole = 0.455 and -0.434 eÅ^{-3} respectively.
7. Please see Figure 1 for atom numbering of **16**. Complete assignment facilitated by the use of NOE, COSY and HETCORR spectroscopy. ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 2.35 and 2.46 (each 1H, d, J = 19 Hz, $C12H_2$), 2.96 and 3.05 (each 1H, d, J = 21 Hz, $C5H_2$), 3.90 (1H, d, J = 10 Hz, C7H), 5.66 (1H, d, J = 10 Hz, C13H), 5.76 (1H, d, J = 10 Hz, C6H), 6.18 (1H, d, J = 5 Hz, C10H), 6.41 (1H, d, J = 6 Hz, C2H), 6.50 (1H, d, J = 10 Hz, C14H), 7.59 (1H, d, J = 5 Hz, C9H), 7.99 (1H, d, J = 6 Hz, C3H); ^{13}C NMR: ($CDCl_3$, 75.5 MHz) δ 39.82 (C5), 43.88 (C7), 47.00 (C12), 47.63 (C8), 121.95 (C14), 122.46 (C6), 128.38 (C13), 133.13 (C10), 137.01 (C2), 140.08 (C4), 152.41 (C9), 167.51 (C3), 204.75 (C11 or C1), 206.81 (C1 or C11); HRMS (EI+): for $C_{14}H_{12}O_2S_2$; calculated 276.0279, observed 276.0266.
8. *Crystal data* for **16**: $C_{14}H_{12}O_2S_2$, M = 276.36, monoclinic, space group $P2_1/n$, a = 9.837(2), b = 5.890(2), c = 21.6728(14) Å, β = 94.219(9)°, V = 1252.4(4) Å^3, Z = 4, D_c = 1.466g cm^{-3}, $F(000)$ = 576, μ(Mo-Kα) = 0.414 mm^{-1}, T = 123 K. Intensities (h k ±l) of a cream coloured prism (dimensions 0.10 x 0.22 x 0.45 mm) were collected by the ω-2θ scan method to $2\theta_{max}$ = 54°. A total of 2905 reflections were collected of which 2746 were unique (R_{int} = 0.0386). Data collected for Lorentz polarization and decay (0.71%) but not for absorption. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms located by difference synthesis were included in the model but not refined. Full-matrix least-squares refinement of 163 parameters gave $R1$ = 0.0356 and $wR2$ = 0.0899 for I ≥ 2σ(I) and $R1$ = 0.0569, $wR2$ = 0.0980, S = 1.036 for all data. The largest difference peak and hole = 0.364 and -0.299 eÅ^{-3} respectively.
9. Spartan, v. 4.0., Wavefunction: Irvine, California, 1995.

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