In the memory of Professor R.R. Gupta

REGIOSELECTIVE SYNTHESIS OF AZABICYCLOADDUCTS DERIVED FROM BENZO[B]THIOPHENE -2, 3 -DIONE AND PIPECOLINIC ACID

S.Verma, K.Arora, D.Jose, R.Joshi, P. Pardasani and R.T. Pardasani*

Department of Chemistry, University of Rajasthan, Jaipur - 302 055, India
email : rtpardasani@gmail.com

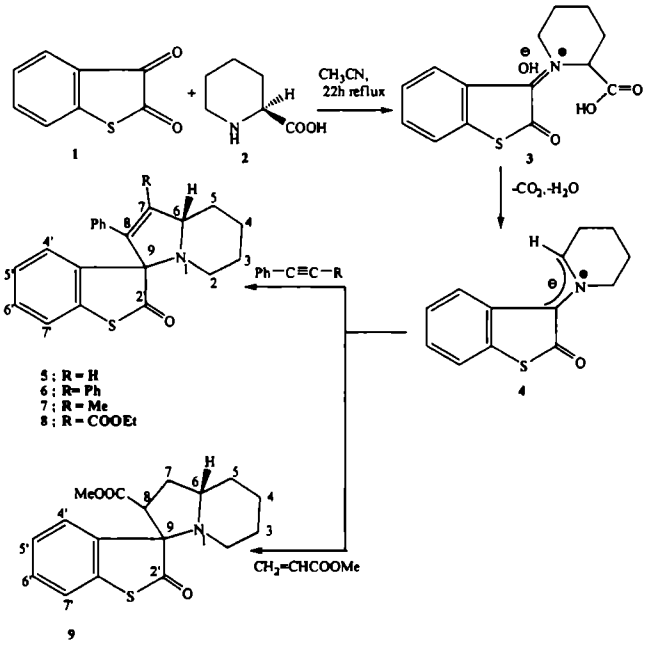
ABSTRACT : A simple and efficient method for the synthesis of novel spiropyrrolidines has been accomplished by regioselective 1, 3-dipolar cycloaddition reactions of azomethine ylide generated by benzo[b]thiophene-2,3-dione and piperidine 2-carboxylic acid in good yield. Molecular orbital calculations have been performed to investigate the regioselectivity of the cycloaddition process.

INTRODUCTION

Heterocyclic compounds have proved to the most inspirable challenge in the area of industrial and pharmaceutical chemistry (1-3). Of the various heterocycles those containing thiophenic nuclei deserve special mention because of their versatile applications in pharmacology (4,5). In the last few decades, the chemistry of α-diones has also been the subject of considerable interest due to their widespread applications in organic synthesis (6,7) and significant biological properties (8,9). Among the various thiophenic derivatives, the most quoted analogue is benzo[b]thiophene-2,3-dione (commonly known as *thioisatin*) (10,11). Synthetically numerous reactions of benzo[b]thiophene-2,3-dione have been described and reviewed (12,13).This remarkable spurt in the literature is attributed to strongly electrophilic C-3 carbonyl group of thioisatin. We have also explored some reactions of thioisatin (14,15) but its 1,3-dipolar cycloaddition reactions have largely remained unexplored. Thus in continuation to our ongoing research program on 1,3-dipolar cycloaddition reaction of various α-diones (16,17), we have applied this strategy to benzo[b]thiophene-2,3-dione and piperidine -2 -carboxylic acid (PCA) to produce bridgehead bicyclic N-heterocycles which may serve as useful precursors for thiophenic drugs.

RESULTS AND DISCUSSION

The reaction of thioisatin **1** with PCA **2** was carried out in equimolar ratio in refluxing dry acetonitrile in the presence of 1-phenyl -1-propyne to afford (6S, 9R) spiro-{8-phenyl-7-melhyl-1-aza-bicyclo [4 3, 0] -7-nonen-9, 3'-benzo[b]thiophene -2'-one **7** in 63% yield. Analogous reactions with other dipolarophiles *viz* phenyl acetylene, diphenyl acetylene, ethyl pheny propiolate and methyl acrylate produced respective cycloadducts **6-9** in 54% to 71% yields (Scheme 1).



SCHEME 1

The mechanism for the formation of cyclodducts **5-9** may involve the initial formation of iminium species **3** followed by the loss of CO_2 *via* stereospecific 1, 3-cycloreversion to azomethine ylide (*amy*) **4** as suggested by Amornraksha *et al* (16). Subsequent [3+2] cycloaddition with various dipolarophiles then produced novel azabicycloadducts. These results are in good agreement with the theoretical calculations as well as those reported by Grigg *et al* (17) for the reaction of carbonyl compounds with amines.

The structures of the cycloadducts **5-9** have been ascertained from their spectral data. Thus IR spectrum of typical 1-phenyl-1-propyne cycloadduct **7** showed characteristic bands at 1700, 1270 and 760 cm^{-1} for >C=O, C-N and C-S stretching vibrations respectively. Its ^1H NMR spectrum showed a singlet at δ2.10 for methylene protons (3-H to 5-H), a singlet at δ 2.55 for methyl protons, a triplet at δ 2.80 for 2-H, a multiplet at δ 2.84 for 6-H; aromatic protons resonated as a multiplet in the range δ7.59-8.459. Its ^{13}C NMR spectrum showed a signal at 182.34 for carbonyl carbon, aromatic carbons appear in the range δ 148.41-131.63, the olefenic carbons resonated at δ 128.48 and 127.43, spiro carbon was noticed at δ 98.28, C-6 at δ 59.86, C-2 at δ 55.73, C-5 at δ 47.73, C-4 at δ 32.94 and C-3 at δ 25.94 and methyl carbon at δ 22.92. The spectral and physical data of all the newly synthesized spirocycloadducts have been given in Table 1.

Quantum Chemical Calculations: Regioselectivity of Cycloaddition

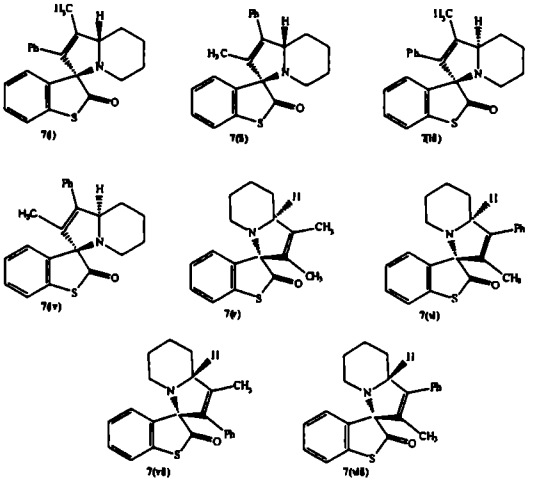
The stereochemical course of the cycloaddition has been examined by AM 1 quantum chemical calculations. Geometry optimization showed that *amy* **3** has an almost planar structure wherein the piperidine ring lies in the same plane as that of thioisatin moiety. It may exist in two isomeric forms: one in which >C=O and C-H of the dipole are *syn* to each other, ***3 syn,*** and the other one in which they are *anti* ,***3 anti***. The ΔH_f, HOMO, LUMO Energies and HOMO-LUMO and LUMO-HOMO energy gaps of azomethine ylide **5** with dipolarophiles are given in Table 2. The transition state of the concerted 1, 3-dipolar cycloaddition reaction is usually controlled by Frontier

Molecular Orbitals (FMO's) of dipolarophiles and dipoles. From Table 2 we may conclude that the $HOMO_{dipole}$-$LUMO_{dipolarophile}$ energy gap is lower than the $LUMO_{dipole}$–$HOMO_{dipolarophile}$ gap and therefore the dominant FMO approach is $HOMO_{dipole}$ – $LUMO_{dipolarophile}$.

Table 2 : ΔH_f, HOMO, LUMO ENERGIES AND H-L AND L-H ENERGY GAPS

	ΔH_f	HOMO (eV)	LUMO (eV)	Energy gaps (eV)	
				H – L	L – H
Dipole Amy 4	24.72	-7.68	-0.70		
Phac	76.40	-9.29	-0.0005	7.67	8.59
Diph	97.65	-8.75	-0.44	7.24	8.05
Phpr	64.78	-9.08	0.03	7.65	8.38
Etph	-11.13	-9.67	-0.67	7.01	8.97
Meac	-69.69	-11.07	-0.04	7.63	10.37

Amy = azomethine ylide, Phac = phenyl acetylene; Diph = diphenyl acetylene; Phpr = 1-phenyl-1-propyne; Etph = ethyl phenyl propiolate; Meac = methyl acrylate



SCHEME 2

Attack of 1-phenyl-1-propyne on the planar azomethine ylide from either side results in the formation of products having three chiral centers (Fig.1). Therefore a total of 2^3 = 8 isomers **7(i-viii)** are possible (Scheme 2).

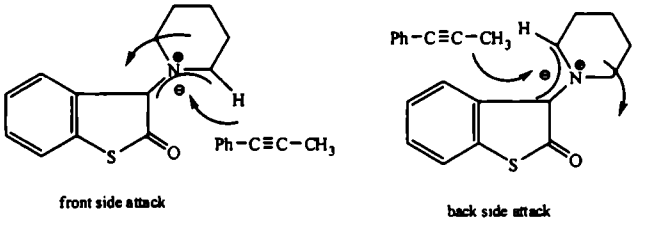


Figure 1: Mode of attack of 1-phenyl-1-propyne on amy 3

We have optimized the geometry of all the eight isomers. Results show that all the eight isomers have almost same ΔH_f, indicating that thermodynamically all are almost equally stable. Frontside attack of 1-phenyl-1-propyne results in the formation of products **6 (v-(viii).** However, in case of this attack, the transition state could not be located even in a single case. This may be attributed to the steric hindrance between the thioisatin ring and piperidine ring because frontside attack would result in the inward movement of the piperidine ring towards the thioisatin ring, making the system unstable and hence failing to produce the transition state geometry. This leaves only the possibility of a back side attack. (Figure 1) Of these possibilities, in two cases 6 (iii) and 6 (iv) where N and H atom on the adjacent carbon atoms do not lie on the same side, the transition state could not be located because a concerted mechanism is not possible in such a situation. This leaves only two structures **6 (i)** and **6 (ii)** for consideration. Out of the remaining two possibilities, we could optimize the transition state in the case of **6 (i)** only. This can be explained using the FMO approach along with the *endo* approach of phenyl ring. The favored path involves the $HOMO_{dipole}$ and the $LUMO_{dipolarophile}$. The results of the above discussion are summarized in Table 3.

Table – 3 : ΔH_fR, ΔH_fTS, ΔH_fP, Ea and stabilization energy of amy with different dipolarophiles

Product	ΔH_fR (Kcal/mol)	ΔH_fTS (Kcal/mol)	ΔH_fP (Kcal/mol)	Ea (Kcal/mol)	Stabilization energy (Kcal/mol)
Amy (4) + phac	101.12	131.14	45.70	30.02	45.42
Amy (4) + phpr	89.50	125.35	49.00	35.85	40.50

EXPERIMENTAL

Analytical and Instrumental details are described elesewhere (14). A Representative method for the synthesis of cycloadduct 7 is described below:

A mixture of thioisatin 1 (0.33 gm; 2.0 mmol), pipecolinic acid 2 (0.26 gm; 2.0 mmol) and 1-phenyl-1-propyne (0.23gm; 2.0mmol) in the equimolar ratio was refluxed in dry acetonitrile (50 ml) for 22 hrs. After completion of the reaction as monitored by TLC, unreacted acid was filtered off and the filtrate was evaporated in *vaccuo* to half volume whereby a brown powder was obtained as the crude product. It was subjected to column chromatography over silica gel and chloroform/ethylacetate 3:1 fraction afforded cycloadduct 7 as brown crystals (0.44 gm; 63%) m.p 210°C.

ACKNOWLEDGEMENT

Sonali Verma is thankful to UGC, New Delhi for RGNF JRF Fellowship.

REFERENCES

1. A. R. Katritzky, C.W. Rees and E. F. V. Scriver Eds.; Comprehensive heterocyclic Chemistry, Part III, Elsevier, New York, 2008.
2. J. A. Joule and K. Mills, Heterocyclic Chemistry, 4th Edn., Blackwell Science, London, 2000, 13.
3. A. R. Katritzky and A. F. Pozharskii, Handbook of Heterocyclic Chemistry, Elsevier, Amsterdam, The Netherlands, 2000.
4. V. Darias, L. Bravo, S. S. Abdallah, C. C. Mateo, M. A. Exposito-Orta, J. Tenerife and J. Manzahares, Arch. Pharm., **325**, 83 (1992).
5. R. J. Fass and V. L. Helsel, Antimicrob. Ag. Chemother. **28**, 834 (1985).
6. J. F. M. da Silva, S. J. Garden and A. C. Pinto, J. Braz. Chem. Soc., **12**, 273 (2001) and references cited therein.
7. M. G. A. Shvekhgeimer, Chem. Heterocycl. Compd. **32**, 249 (1996).
8. S. N. Pandeya, S. Smitha, M. Jyoti and S. K. Sridhar, Acta Pharm., **55**, 27 (2005).
9. S. N. Pandeya, D. Sriram, G. Nath and E. DeClércq, Eur. J. Pharm. Sci., **9**, 25 (1999).
10. G. Carrona and S. Palazzo, Gazz. Chem. Ital **98**, 911 (1968).
11. B. D. Tilak, Tetrahedron, **9**, 76 (1960).
12. M. Rajopadhye and Frank D. Popp, Heterocycles, **27**, 1489 (1988).
13. J. Tatsugi and N. Shimazaki, Phosphorus, Sulphur, Silicon and The Related elements, **180**, 1433, (2005).
14. A. V. Londhe, B. Gupta. S. Kohli, P. Pardasani and R.T. Pardasani, Z. Naturoforsch. B. **61b**, 213 (2006).
15. R. T. Pardasani, P. Pardasani, I. Sharma, A. Londhe and B. Gupta, Phosphorus, Sulphur, Silicon and The Related Elements, **179**, 2549, (2004).
16. K. Amornraksha, R. Grigg, H. Q. N. Gunaratna, J. Kemp and V. Sridharan, J. Chem. Soc., Perkin Trans., 2285 (1987).
17. H. Ardill, R. Grigg. J. F. Malone, V. Sridharan and W.A. Thomas, Tetrahedron, **50**, 5067 (1994)

Received on 20 February, 2009.

Table 3 : PHYSICAL AND SPECTRAL DATA OF AZABICYCLOADDUCTS 5-9

Comp No.	Physical state	Molecular formula	Yield	Elemental analysis calcd/found				IR (cm-^{1})	^{1}H NMR (δ, ppm)	^{13}C NMR (δ, ppm)
				C	H	N	S			
5	Choclate brown	$C_{21}H_{19}NOS$	54%	75.67 (74.32)	5.70 (4.78)	4.20 (3.98)	9.60 (8.98)	3040m(C-H_{aro}), 2910m (C-H_{alk}), 1710s(>C=O), 1285m(C-N), 690w (C-S)	δ 2.17 (s, 3-H +4-H +5-H, 6H), 2.25 (t, 2-H, 2H) 2.36, (d 7-H, 1H), 3.33 (q, J = 7.25 Hz, 6-H, 1H), 7.16 – 7.97 (m, 8H, 5 ArH + 7'H, 6'H, 4'H)	-
6	Shiny brown solid	$C_{27}H_{23}NOS$	69%	79.21 (78.38)	6.05 (5.58)	4.03 (3.97)	9.21 (8.45)	3060m(C-H_{aro}), 2940m (C-H_{alk}), 1690s(>C=O), 1290m(C-N), 765w (C-S)	δ 2.15 (s, 3-H +4-H +5-H, 6H), 2.50 (t, 2-H, 2H) 2.74, (t 6-H, 1H), 7.20 – 8.04 (m, ArH)	-
7	Dark brown	$C_{22}H_{21}NOS$	63%	76.08 (75.93)	6.05 (5.85)	4.03 (3.86)	9.20 (8.32)	3020m(C-H_{aro}), 2850m (C-H_{alk}), 1700s(>C=O), 1270m(C-N), 760w (C-S)	δ 2.10(s, 3-H+4-H+5-H, 6H) 2.55 (s, CH_3, 3H), 2.80 (t, 2-H, 2H) 2.84, (m, 6-H, 1H), 7.59–8.45(m, ArH, 9H)	δ 182.34 (C=O), 148.41 – 131.63 (ArC), 128.48, 127.43 (C=C), 98.28 (spiro C-9), 59.86 (C-6), 55.73 (C-2), 47.73 (C-5), 32.94 (C-4), 25.94 (C-3), 22.92 (CH_3)
8	Brown powder	$C_{24}H_{23}NO_3S$	65%	71.11 (70.03)	5.68 (4.54)	3.46 (3.01)	7.90 (6.69)	3050m(C-H_{aro}), 1660s(O-C=O), 1640sh(>C=O), 1280m(C-N), 1215m (C-O), 650w (C-S)	δ 1.20 (s, CH_3), 2.14 (s, 3-H +4-H +5-H, 6H), 2.23 (br t, 2-H, 2H) 2.46, (t, 6-H, 1H), 3.75 (q, OCH_2) 6.59 – 7.58 (m, 8H, 5 ArH+ 7'H, 6'H, 4'H)	29δ 186.44 (C=O), 181.28 (C=O) 138.14 – 126.12 (ArC), 126.46, 124.52 (C=C), 88.34 (Spiro C-9), 61.46 (C-6), 52.86 (OCH_2), 49.46 (C-2), 39.46 (C-5),.70 (C-4) 23.96 (C-3), 19.47 (CH_3)
9	Red crystal	$C_{17}H_{18}NO_3S$	71%	64.55 (63.68)	4.87 (4.53)	8.53 (7.79)	9.75 (9.32)	3050m(C-H_{aro}), 2920m(C-H_{alk}), 1760s(O-C=O), 1720s(C=O), 1300m(C-N), 1245m (C-O), 775w (C-S)	δ 2.84, (s, 3-H +4-H +5-H, 6H), 2.56 (t, 2-H, 2H) 2.58, (t, 6-H, 1H), 3.32 (t, 7-H, 2H) 4.34 (t, 8-H, 1H), 4.45 (s, OCH_3) 7.49-7.94(m, ArH)	-