COMMUNICATION

Regioselective synthesis of heterocycles by sigmatropic rearrangement: passage to 3,11a-dimethyl-6a,11a-dihydro-1*H*,6*H*-pyrano[3′,4′:5,6]thiopyrano[4,3-*b*][1]benzofuran-1-one †

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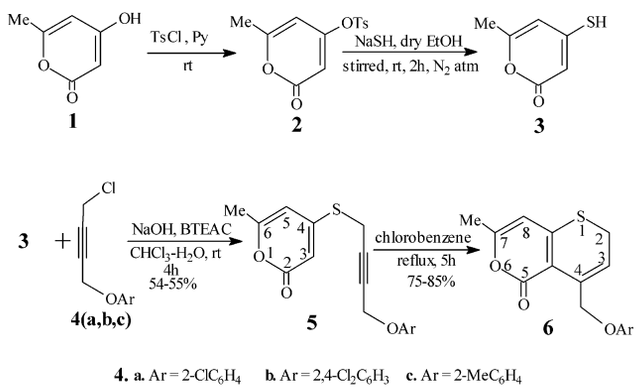
Received (in Cambridge, UK) 28th June 2002, Accepted 12th August 2002
First published as an Advance Article on the web 30th August 2002

A number of hitherto unreported 3,11a-dimethyl-6a,11a-dihydro-1*H*,6*H*-pyrano[3′,4′:5,6]thiopyrano[4,3-*b*][1]benzofuran-1-ones **11a**,**b**,**c** have been synthesized in good yields (60–67%) by the thermal rearrangement of 4-aryloxymethyl-7-methylthiopyrano[3,2-*c*]pyran-5-ones **6a**,**b**,**c**. Compounds **6a**,**b**,**c** were in turn synthesized in 75–85% yields by the thermal rearrangement of 4-(4′-aryloxybut-2′-ynylthio)-6-methylpyran-2-ones **5a**,**b**,**c**. Compounds **5a**,**b**,**c** were obtained in 54–55% yields by the phase-transfer catalysed alkylation of 4-mercapto-6-methyl-2-pyrone **3** with 1-aryloxy-4-chlorobut-2-yne **4a**,**b**,**c**.

The 4-hydroxy-6-methyl-2-pyrone (triacetic acid lactone) moiety is important in its occurrence in a number of naturally occurring compounds.[1] Some of these natural products contain biogenetically plausible groups at C3 or C5 or both. Elasnin, isolated from *Steptomyces* sp., for example, is a specific inhibitor of human leucocyte elastase, an enzyme involved in inflammatory processes such as pulmonary emphysema.[2] As a logical extension, many more simple pyrones structurally analogous to elasnin have been synthesized and evaluated as inhibitors of several elastases.[3] Some 4-hydroxy-2-pyrones have also been tested as anticoagulant agents.[4] As a continuation of our interest in the synthesis of bioactive heterocycles[5] by the application of sigmatropic rearrangements,[6] we recently reported the synthesis of fused pyranopyrone[7] and pyridopyrone[8] polyheterocycles. These successful syntheses demanded that our endeavour be directed towards the utilization of this novel methodology in order to determine a convenient route to the corresponding sulfur analogues.

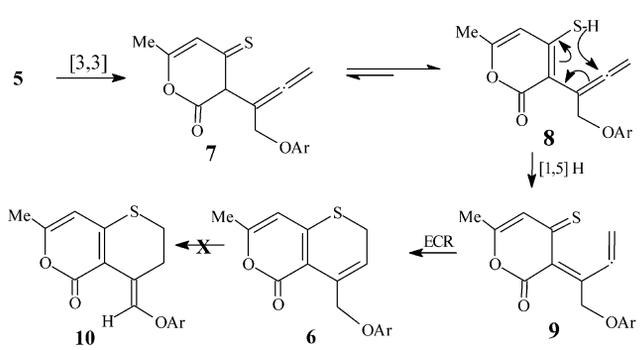
The starting materials for this investigation, 4-(4′-aryloxybut-2′-ynylthio)-6-methylpyran-2-ones **5a**,**b**,**c** were synthesized by treating 4-mercapto-6-methylpyran-2-one **3** with 1-aryloxy-4-chlorobut-2-yne **4a**,**b**,**c** at room temperature under phase transfer catalysis conditions using benzyltriethylammonium chloride (BTEAC). Compounds **5a**,**b**,**c** were characterised from their spectroscopic data and elemental analysis. Compound **3**, in turn, was prepared by the reaction of 6-methyl-4-tosyloxypyran-2-one[9] **2** with NaSH in dry ethanol at room temperature under a nitrogen atmosphere (Scheme 1).

Substrates **5a**,**b**,**c** are endowed with a vinyl propargyl ‡ sulfide moiety as well as an aryl propargyl ether segment. Compounds with this structural feature are expected to be prone to thermal [3,3] sigmatropic rearrangements. Thus compounds **5a**,**b**,**c** offer excellent scope for the study of competition between oxy- and thio-Claisen rearrangements as well as the synthesis of new heterocycles. With these premutations, substrate **5a** was refluxed in chlorobenzene (131–132 °C). A change was observed by TLC within 30 min. The starting material completely disappeared to give a pale yellow solid (mp 126–127 °C) in 5 h (TLC monitoring). The structure of product **6a** was ascertained from its elemental analysis and spectroscopic data. The pmr spectrum of compound **6a** displayed a two-proton doublet at δ 3.38 (J 6 Hz) due to C_2-*H* and a one-proton triplate at δ 6.12 (J 6Hz) assignable to C_3-*H*. It is noteworthy that in the synthesis of pyranopyrone derivatives from 4-(4′-aryloxybut-2′-ynyloxy)-6-methylpyran-2-ones, only exocyclic products corresponding to **10** were obtained.[7] Synthesis of pyridinopyrone heterocycles from 4-(*N*-4′-aryloxybut-2′-ynyl)-*N*-methylamino-6-methylpyran-2-ones also afforded chiefly the exocyclic derivatives along with the endocyclic compounds as minor products corresponding to **6** only in three cases.[8]



Scheme 1

Formation of **6** from **5** can be mechanistically devised as outlined in Scheme 2. [3,3] Sigmatropic rearrangement at the vinyl propargyl sulfide moiety of compound **5** furnished the allenyl intermediate **7**. Intermediate **7** may undergo tautomerisation to generate **8**. A [1,5] H shift in **8** may give **9**. 6π Electrocyclic ring closure in **9** may finally afford product **6**.



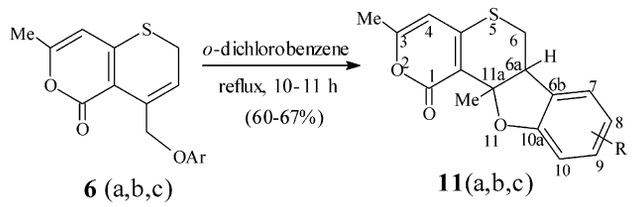
Scheme 2

Compound **6** still possesses an aryl allyl ether moiety and so it is expected to undergo a thermal [3,3] sigmatropic rearrangement. We, therefore, subjected compound **6a** to thermal rearrangement in refluxing *o*-dichlorobenzene (179–181 °C) and the isolated product was shown to be compound **11a** from its elemental analysis and spectroscopic data (Scheme 3). Two C_6-*H* and the C_{6a}-*H* appeared as three one-proton doublet of doublets at δ 2.88 (J 9.9, 13.5 Hz), 3.05 (J 3.9, 13.5 Hz) and 3.57 (J 3.9, 9.9 Hz). Compounds **6b**,**c** were similarly treated to obtain compounds **11b**,**c**.

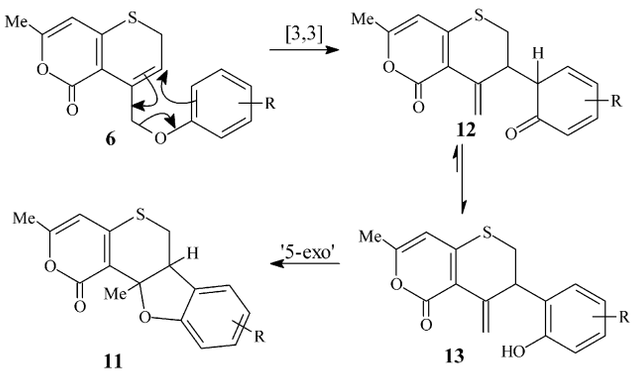
Formation of **11** from **6** can be rationalized as shown in Scheme 4. [3,3] Sigmatropic rearrangement in **6** may produce

† Electronic supplementary information (ESI) available: General experimental procedures. See http://www.rsc.org/suppdata/p1/b2/b206287a/

DOI: 10.1039/b206287a



Scheme 3



Scheme 4

intermediate **12**. Intermediate **12** may tautomerize to **13** which, on '5-exo' ring closure, should give compound **11**.

Substrates **5a**,**b**,**c** underwent [3,3] sigmatropic rearrangement at the vinyl propargyl sulfide segment instead of the aryl propargyl ether moiety. A lesser energy requirement for the sigmatropic rearrangement in vinyl propargyl systems[10] compared to that in aryl propargyl moieties[11] may be responsible for this regioselectivity. Thiopyranopyrone derivatives **6a**,**b**,**c** were exclusively obtained in all cases. Thio-Claisen rearrangement of aryl propargyl sulfide is known to give a mixture of two products *viz.* 2*H*-thiochromene and 2-methylthianaphthalene.[12] Thio-Claisen rearrangement of heterocyclic substrates is also known to be accompanied by a [1,3] radical shift.[13] However in the present instance none of the examples gave a mixture of products which is again a general phenomenon shown by earlier workers.[14]

In conclusion, we have successfully exploited thermal sigmatropic rearrangements as an expedient avenue towards the synthesis of fused furanothiopyran heterocyclic ring systems. This type of ring system is otherwise difficult to construct. The synthetic approach adopted here may be considered as a mild and facile pathway for the synthesis of fused furanothiopyran heterocyclic systems.

Acknowledgements

We thank the CSIR (New Delhi) for financial assistance and the University of Kalyani for laboratory facilities.

References

‡ The IUPAC name for propargyl is prop-2-ynyl.

1 (*a*) R. Bentley and P. M. Zwitkowits, *J. Am. Chem. Soc.*, 1967, **89**, 676; (*b*) R. Bentley and P. M. Zwitkowits, *J. Am. Chem. Soc.*, 1967, **89**, 681.
2 (*a*) S. Omura, H. Ohno, T. Saheki, Y. Masakazu and A. Nakagawa, *Biochem. Biophys. Res. Commun.*, 1978, **83**, 704; (*b*) H. Ohno, T. Saheki, J. Awaya, A. Nakagawa and S. Omura, *J. Antibiot.*, 1978, **31**, 1116.
3 (*a*) W. C. Groutas, W. R. Abrams, R. T. Carrol, M. K. Moi, K. E. Miller and M. T. Margolis, *Experientia*, 1984, **40**, 361; (*b*) W. C. Groutas, M. A. Stanga, M. J. Brubaker, T. L. Huang, M. K. Moi and R. T. Carrol, *J. Med. Chem.*, 1985, **28**, 1106; (*c*) R. W. Spencer, L. J. Copp and J. R. Pfister, *J. Med. Chem.*, 1985, **28**, 1828; (*d*) L. Cook, B. Ternai and P. Ghosh, *J. Med. Chem.*, 1987, **30**, 1017.
4 (*a*) K. Rehse, W. Schinkel and U. Siemann, *Arch. Pharm.*, 1980, **313**, 344; (*b*) K. Rehse and W. Schinkel, *Arch. Pharm.*, 1983, **316**, 845; (*c*) K. Rehse and W. Schinkel, *Arch. Pharm.*, 1983, **316**, 988; (*d*) K. Rehse and F. Brandt, *Arch. Pharm.*, 1983, **316**, 1030.
5 (*a*) K. C. Majumdar, U. Das and N. K. Jana, *J. Org. Chem.*, 1998, **63**, 3550; (*b*) K. C. Majumdar and T. Bhattacharyya, *Tetrahedron Lett.*, 2001, **42**, 4231.
6 (*a*) K. C. Majumdar and P. Biswas, *Tetrahedron*, 1998, **54**, 11603; (*b*) K. C. Majumdar and P. Biswas, *Tetrahedron*, 1999, **55**, 1449; (*c*) K. C. Majumdar and S. K. Samanta, *Tetrahedron*, 2001, **57**, 4955; (*d*) K. C. Majumdar and U. Das, *J. Org. Chem.*, 1998, **63**, 9997.
7 K. C. Majumdar, S. Ghosh and A. K. Kundu, *Synth. Commun.*, 2002, **32**, 753.
8 K. C. Majumdar and S. Ghosh, *Tetrahedron*, 2001, **57**, 1589.
9 A. M. Bittencourt, O. R. Gottlieb, W. B. Mors, M. Taveira Magalhaes, S. Mageswaran, W. D. Ollis and I. O. Sutherland, *Tetrahedron*, 1971, **27**, 1043.
10 K. C. Majumdar, A. T. Khan and R. N. De, *Synth. Commun.*, 1988, **18**, 1589.
11 (*a*) J. Zsindely and H. Schmidt, *Helv. Chim. Acta*, 1968, **51**, 1510; (*b*) K. C. Majumdar, B. S. Thyagarajan and K. K. Balasubramanian, *J. Heterocycl. Chem.*, 1973, **10**, 159; (*c*) L. Claisen, *Ber.*, 1912, **45**, 3157.
12 H. Kwart and T. J. George, *J. Chem. Soc., Chem Commun.*, 1970, 433.
13 K. C. Majumdar, N. K. Jana, A. Bandyopadhya and S. K. Ghosh, *Synth. Commun.*, 2001, **31**, 93.
14 (*a*) L. Brandsma and H. J. Y. Bos, *Rec. Trav. Chim. Pays-Bas*, 1969, **88**, 732; (*b*) L. Brandsma and Schuiji Largos, *Rec. Trav. Chim. Pays-Bas*, 1970, **89**, 110.