Tetrahedron Letters, Vol. 34, No. 48, pp. 7705-7708, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Carbanion Methodology for Alkylations and Acylations in the Synthesis of Substituted Oxazoles. The Formation of Cornforth Rearrangement Products.

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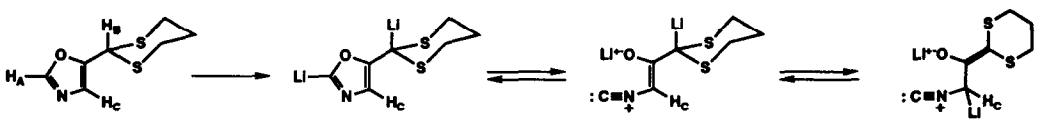
Key Words: oxazole synthesis; Cornforth rearrangement

Abstract: *Studies of monoalkylation of the dianion generated from 2-(5-oxazolyl)-1,3-dithiane 1 led exclusively to substitution adjacent to sulfur. However, acylation reactions of 1 afforded 4,5-disubstituted oxazoles as novel examples of direct acylation of the oxazole nucleus.*

Considerable effort has documented methods for cyclization and dehydration to generate the oxazole nucleus bearing 2,4-disubstitution and 2,4,5-trisubstitution.[1,2] Procedures for the preparation of 4- or 5-monosubstituted oxazoles, or 4,5-disubstituted cases are more limited in scope. Recent investigations have examined the chemistry of metalated intermediates of a preformed oxazole nucleus. Reports by Rickborn,[3] Dondoni,[4] and Hodges[5] have shown that hydrogen attached at C-2 of oxazole is most acidic ($pK_\alpha \cong 20$). The 2-lithiooxazole is in equilibrium with the ring-opened isonitrile enolate, affording ambident nucleophilicity. A more facile deprotonation of various 2-methyloxazoles (at the C-2 α-position) has provided a stable metalated intermediate for synthesis.[6,7] However, Meyers has reported one case in which substituent effects lead to anomalous metalation.[8]

Owing to our interests in oxazole-containing natural products, we have been concerned with the preparation of oxazoles which are unsubstituted at the C-2 position. Our study has described the behavior of anions of 2-(5-oxazolyl)-1,3-dithiane[9] 1 for a variety of alkylation and acylation reactions. Deprotonation of 1 with *n*-butyllithium (1.5 equivs) at -78 °C in THF solely provided deuterium (D_2O) incorporation at C-2 (H_A). An additional one equivalent of strong base (*n*-BuLi or LiHMDS) with stirring for one hour also provided complete deuterium exchange of H_B. Excess base (>5.0 equivs.) did not produce deuterium replacement of H_C (D_2O quench at -20 °C).

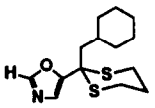
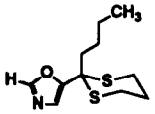
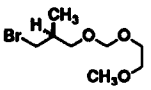
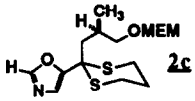
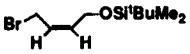
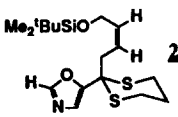
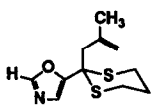
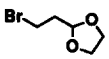
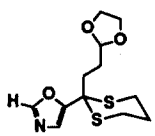


1 1a 1b 1c

Anticipating ambident nucleophilic character of the dianion 1a as expressed by 1b and 1c, a survey of reactions with a variety of electrophiles was undertaken.

A study of alkylations of the dianion of 1 are summarized in Table I. All reactions occurred at -78 °C with monoalkylation at the carbanion location adjacent to the heteroaromatic ring. Allylic, benzylic and primary alkyl bromides and iodides afforded good yields of C-5 substituted oxazoles following flash chromatography. The use of secondary alkyl halides led only to the recovery of starting oxazole 1. Highly reactive electrophiles,

Table I. A Survey of Alkylations of Oxazole 1.

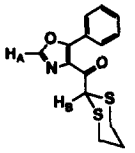
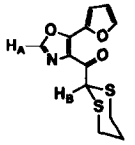
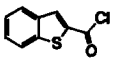
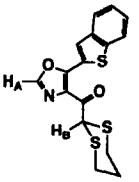
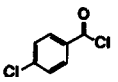
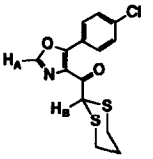
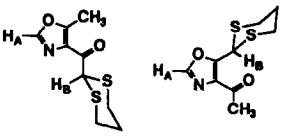
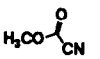
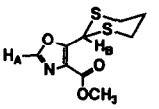
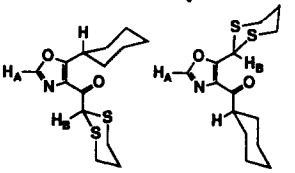
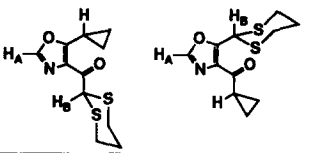
Entry	Electrophile[a]	Product		Yield
1			2a	71%
2			2b	82%
3			2c	78%
4			2d	53%
5			2e	88%
6			2f	65%

[a] **Conditions:** LiHMDS (3.0 equiv.) in THF/DMPU (ratio 1:1) at -78 °C with 1; then addition of electrophile (5 equiv.) and stir at -78 °C for 30 min.; quench with aqueous LiCl at -78 °C. Products were purified by column chromatography on silica gel.

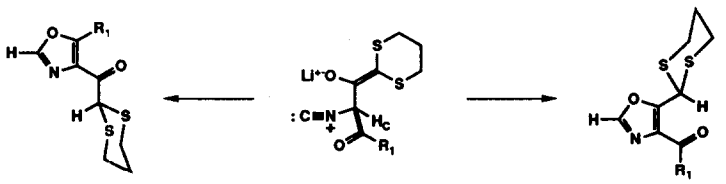
such as CH_3I and TMS-Cl, gave complex mixtures resulting from C- and O-alkylations of the ring-opened forms 1b and 1c.[4]

Acylations of the dianion of 1 followed a different course affording the 4,5-disubstituted oxazoles illustrated in Table II. Interestingly, structural elucidations of the major products demonstrated insertion of a carbonyl unit between the oxazole ring and the dithiane. Direct acylation of the 2-position of oxazole 1 (H_A) or acylation of the 1,3-dithianyl anion (H_B) was not observed. These products are consistent with a rationale which suggests selective C-acylation of the ring-opened tautomer 1c.[10] Intermediate isonitriles 1d may provide ring closure with participation of either carbonyl oxygen to yield isomeric oxazoles 3 and 4.

Table II. Base-Induced Acylation Reactions of Oxazole 1.

Entry	Electrophile[a]	Product(s)	Product Ratios	Yield %	Characteristic ^{1}H-NMR Data
1			3a only	74%	3a H_A δ = 7.87 H_B δ = 5.46
2			3b only	55%	3b H_A δ = 7.81 H_B δ = 5.39
3			3c only	84%	3c H_A δ = 7.84 H_B δ = 5.43
4			3d only	47%	3d H_A δ = 7.85 H_B δ = 5.42
5			3e/4e = 3:2	85%	3e H_A δ = 7.70 H_B δ = 5.23 4e H_A δ = 7.80 H_B δ = 5.92
6			4f only	84%	4f H_A δ = 7.85 H_B δ = 5.85
7			3g/4g = 2.75:1	94%	3g H_A δ = 7.67 H_B δ = 5.23 4g H_A δ = 7.80 H_B δ = 5.96
8			3h/4h = 1:1.8	98%	3h H_A δ = 7.56 H_B δ = 5.24 4h H_A δ = 7.84 H_B δ = 5.97

[a] **Conditions:** LiHMDS (3.0 equiv.) in THF at -78 °C with 1; then addition of electrophile (5 equiv.) and stir at -78 °C → 0 °C. Quench with aqueous NH_4Cl. Individual isomers were separated by silica gel chromatography.



3 1d 4

Such behavior corresponds to the known thermal Cornforth rearrangements of trisubstituted 4-acyl-5-amino/alkoxyoxazoles.[11] However, our literature search has not uncovered examples of the Cornforth rearrangement under base-induced, low-temperature conditions. Resubmission of the individual pure oxazoles 3e and 4e to lithium bis(trimethylsilyl)amide (5.0 equivs) at -78 °C in THF with gradual warming to 0 °C over three hours (quench with aqu. NH_4Cl at 0 °C) established thermodynamic control (ratio 3e/4e = 3:2) for the formation of this 4,5-disubstituted example.[12]

In summary, a study of the chemistry of dianions derived from a parent oxazole has led to the preparation of a series of novel functionalized oxazoles. Further efforts for natural product synthesis are underway.

Acknowledgement: We thank the National Institutes of Health (GM-42897) for financial support of this research.

References:

1. Reviews include: *Heterocyclic Compounds: Oxazoles,* Turchi, I.J., Ed. John Wiley and Sons, New York, **1986**, *45*, 1-341. Boyd, G.V. "Oxazoles and Their Benzo Derivatives" in *Comprehensive Heterocyclic Chemistry*, Vol. 6, Potts, K.T., Ed. Pergamon Pres, N.Y., **1984**, 177-233.
2. For some recent reports: Williams, E.L. *Tetrahedron Lett.* **1992**, *33*, 1033. Yoo, S.-K. *Tetrahedron Lett.* **1992**, *33*, 2159. Gangloff, A.R.; Akermark, B.; Helquist, P. *J. Org. Chem.* **1992**, *57*, 4797. See also: Evans, D.A.; Gage, J.R.; Leighton, J.L. *J. Am. Chem. Soc.* **1992**, *114*, 9434.
3. Whitney, S.E.; Rickborn, B. *J. Org. Chem.* **1991**, *56*, 3058.
4. Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *J. Org. Chem.* **1987**, *52*, 3413.
5. Hodges, J.C.; Patt, W.C.; Connolly, C.J. *J. Org. Chem.* **1991**, *56*, 449.
6. Examples include: Kozikowski, A.P.; Ames, A. *J. Org. Chem.* **1980**, *45*, 2548. Lipshutz, B.H.; Hungate, R.W. *J. Org. Chem.* **1981**, *46*, 1410.
7. Stabilized 4-oxazolylmethylides have recently been used in Wittig reactions. Zhao, Z.; Scarlato, G.R.; Armstrong, R.W. *Tetrahedron Lett.* **1991**, *32*, 1609.
8. Meyers, A.I. Lawson, J.P. *Tetrahedron Lett.* **1981**, *22*, 3163.
9. Schregenberger, C.; Seebach, D. *Liebigs Ann. Chem.* **1986**, 2081.
10. Reactive alkyl acid chlorides (for example: acetyl chloride and methyl chloroformate; entries 5 and 6 of Table II) led to complex product mixtures from which O-acylated isonitriles could be isolated. For the preparation of acylcyanides: Hünig, S.; Schaller, R. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 36. Our acyl cyanides were distilled prior to use.
11. Dewar, M.J.S.; Turchi, I.J. *J. Am. Chem. Soc.* **1974**, *96*, 6148. Dewar, M.J.S.; Turchi, I.J. *J. Org. Chem.* **1975**, *40*, 1521.
12. All products were purified and fully characterized. As an aside, we have performed energy minimization calculations of 3e and 4e. The AM1 Hamiltonian used in MOPAC 6.0/QCPE program #455 (Department of Chemistry; Indiana University; Bloomington, IN 47405) revealed an energy difference of 1.1 kcal/mol favoring 3e. The C_4-carbonyl of 3e is coplanar with the heterocyclic ring and *anti* to nitrogen. In structure 4e, this conjugation is perturbed by steric interaction with the adjacent dithane at C_5. Calculations of 3a indicate that the C_5-phenyl unit is orthogonal to the hetero-aromatic system as expected in analogous biphenyl systems. We thank Nancy L. Brichford for these efforts.

(Received in USA 3 August 1993; accepted 23 September 1993)