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AN ADDITION-ELIMINATION STRATEGY FOR THE SYNTHESIS OF OXAZOLES

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Abstract: N-acylpropargylamines have been regioselectively converted to (E)-β-iodo(vinyl)sulfones which, in turn, were converted to 2,5-disubstituted oxazoles by base treatment.

Truce reported the functionalization of terminal alkynes to (E)-β-iodo(vinyl)sulfones (1), and that these moieties underwent facile substitution reactions with organocopper reagents (Scheme 1)[1,2a].

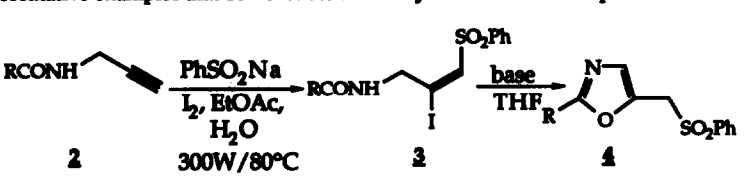
1

Scheme 1

Subsequent exploitation of the (E)-β-iodo(vinyl)sulfone group to gain access to vinyl and alkynyl sulfones followed[2b]. Recently, Back[3] has extended this concept to the development of β-phenylseleno(vinyl) sulfones, versatile moieties that can be elaborated to allenic- and alkynyl sulfones.

The ease in which (E)-β-iodo(vinyl)sulfones are prepared from terminal alkynes warrants further exploration of their synthetic potential. We report here our initial studies on their use in heterocyclic synthesis.[4]

N-acylpropargylamines (2) are regioselectively converted to (E)-β-iodo(vinyl)sulfones (3) with sodium benzenesulfinate and I_2 in ethyl acetate and water[2b]. The reaction is illuminated with a 300W lamp in close enough proximity to sustain a steady reflux. Reactions of the amides (3) with a variety of bases yielded oxazole products (4) (Scheme 2)[5]. Representative examples that demonstrate the utility of this method are presented in Table 1.

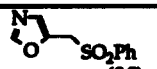
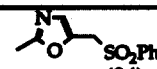
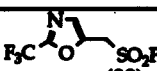
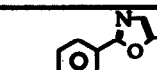
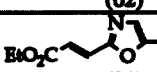
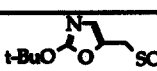


2 3 4

Scheme 2

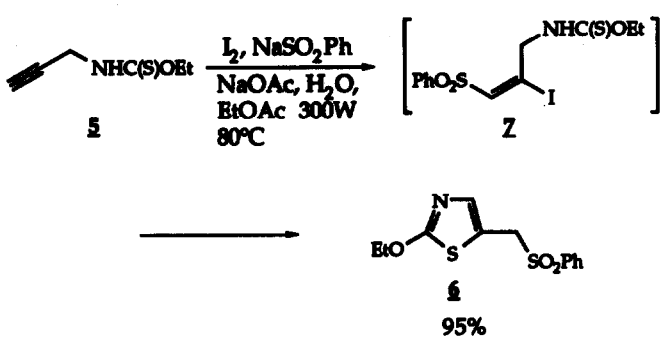
The drive for aromatization and the propensity[2b] of α,β-unsaturated sulfones to isomerize to β,γ-unsaturated sulfones under basic conditions probably contributes to the mildness of this cyclization reaction. The wide variety of substituents tolerated in this cyclization as well as the synthetic potential of the sulfonyl methylene moiety in the oxazole product [6a] adds to the utility of this procedure[6b].

Table 1: Synthesis of Oxazoles (4) from Sulfones (3)

Entry	Sulfone (3) (% yield)[i] from 2	Oxazole (4) (% yield)[i,ii]	Base/Reaction Temp. °C/Reaction Time
a	R = H (44)	 (95)	LiN(TMS)$_2$/0°/2hr.
b	R = Me (38)	 (94)	NaH/0°/0.75hr.
c	R = CF_3 (52)	 (90)	i-Pr$_2$NEt/0° for 3.5hr. then 65° for 0.5hr.
d	R=MeO  (60)	 (62)	NaH/65°/2hr.
e	R=EtO$_2$C  (61)	 (91)	i-Pr2NEt/ 65°/3hr.
f	R = t-BuO (98)	 (66)	NaH/0°/0.75hr.

i: All yields are of isolated materials and are unoptimized
ii: All new compounds were characterized by 300 MHz ^{1}H n.m.r., ^{13}C n.m.r., I.R., C.I. mass spectrometry and microanalysis.

Further investigations led us to prepare the thiocarbamate (5). Exposure of (5)[7] to the standard conditions described earlier produced thiazole (6)[8] in nearly quantitative yield (Scheme 3). The intermediate olefin (7) appears to spontaneously cyclize under the reaction conditions.



5 7 6

95%

Scheme 3

In conclusion, we have demonstrated an efficient method for the synthesis of oxazoles and thiazoles, starting

from inexpensive and commercially available materials.

ACKNOWLEDGEMENTS

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2. a) Truce, W. E.; Borel, A. W.; Marek, P. J. J. Org. Chem., 1976, 41 401.
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3. a) Back, T. G.; Krishna, M. V.; Muralidharan, K. R. J. Org. Chem. 1989, 54, 4146.
   b) Back, T. G.; Lai, E. K. Y.; Muralidharan, K. R. Tetrahedron Lett. 1989, 30, 6481.
   c) Back, T. G.; Lai, E. K. Y.; Muralidharan, K. R. J. Org. Chem. 1990, 54 4595.

4. Padwa recently reported that suitably substituted E-β-iodo (vinyl) sulfones, prepared from the reaction of allenes with iodine, undergo intramolecular addition-elimination reactions to form 2,3,4-trisubstituted furans. See: Padwa, A.; Austin, D. J.; Ishida, M.; Muller, C. L.; Murphree, S. S. and Yeske, Y. E. J. Org. Chem. 1992, 57, 1161.

5. A representative procedure is as follows:
   To a rapidly stirred mixture of propargylformamide (2(a)), (2.041 g, 24.6 mmol.) in ethyl acetate (80 ml) and water (60 ml) was sequentially added sodium acetate (2.96 g, 36 mmol) sodium benzenesulfinate (7.91 g, 48 mmol) and iodine (6.55 g, 26 mmol). The mixture was illuminated with a 300W lamp for 35 minutes, then quenched with 1M $Na_2S_2O_3$. The organic layer was dried ($MgSO_4$), filtered and evaporated to a residue (5.4 g), which was then chromatographed on silica gel using hexane : ether (2:1) as eluent. This gave the required sulfone (3(a)), (3.76 g, 44%) as colorless crystals(mp. 156-157°C from Et_2O/hexane). Anal. Calcd.for $C_{10}H_{10}INO_3S$: C, 34.20; H, 2.87; N, 3.99; S, 9.13. Found: C, 34.16; H, 2.83; N, 3.91; S, 9.24. To sulfone (3(a)) (0.2 g., 0.57 mmol.) in dry THF (4 ml.) and DMSO (0.5 ml.) at 0°C under argon was added lithium bis(trimethylsilyl)amide (1.0 M in THF, 0.68 mmol.). After 40 minutes, the brown mixture was diluted with ether and quenched with 1N HCl. The organic phase was washed with sat. $NaHCO_3$ (2x), and brine, then dried ($MgSO_4$), filtered and evaporated to a residue (0.16 g). This was chromatographed on silica gel using hexane : ether (1:1) as eluent, giving the required oxazole (4(a)) (0.12 g, 95%) as colorless crystals (m.p. 101-103°C (Et_2O/hexane)); ^1H NMR (300 MHz, $CDCl_3$) δ 4.49 (s, 2H, CH_2SO_2Ph), 6.97 (s, 1H, H-4), 7.52-7.78 (m, 5H, Ar-H), 7.82 (s, 1H, H- 2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 53.24 (CH_2SO_2Ph), 128.02, 128.35, 129.29, 134.29 (Ar C's), 137.50, 140.57 (C-4, C-5), 151.98 (C-2); IR(KBr) 1322, 1152 cm^{-1}; Anal. Calcd for $C_{10}H_9NO_3S$: C, 53.80; H, 4.06; N, 6.27; S, 14.36. Found: C, 53.21; H, 3.96; N, 6.13; S 14.22.

6. a) For the deprotonation/acylation of (phenylsulfonyl)methyl substituent at oxazole C-2 position, see: Nagao, Y.; Yamada, S.; Fujita, E. Tetrahedron Lett. 1983, 24, 2287.
   b) For a comprehensive review on oxazoles, see "Chemistry of Heterocyclic Compounds" Vol. 45: Oxazoles; Turchi, I. J. ed.; John Wiley and Sons Inc., New York, 1986.

7. Prepared from propargylamine in 80% yield (b.p. 135-140°C (9 mmHg)) Scully, F. E. Jr.; Ortega, T. J. Org. Chem. 1989, 54, 2978.

8. M. p. 84-86°C; Anal. Calcd. for $C_{12}H_{13}NO_3S_2$: C, 50.87; H, 4.62; N, 4.94; S, 22.63. Found : C, 51.12; H, 4.64; N, 4.71; S, 22.51.

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