Pergamon

Tetrahedron Letters, Vol. 36, No. 3, pp. 467-470, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(94)02288-7

Single Step Stereospecific Transformation of 2-Phenylthio Secondary Amides into *(Z)*-3-Chloro-2-Phenylthio Acrylamides

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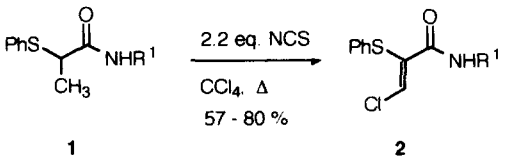
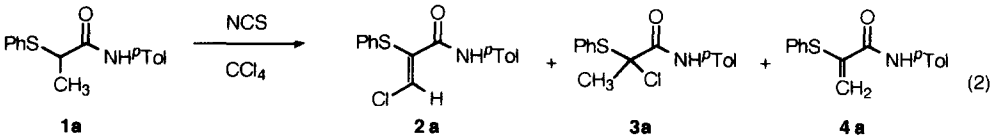
Abstract: α-Phenylthio secondary propanamides **1a-e** are converted stereospecifically on treatment with NCS to the analogous *(Z)*-α-phenylthio-β-chloro propenamides **2a-e**. Extension to longer chain secondary amide derivatives **1f-g** is also possible, albeit less efficiently and without any appreciable stereoselectivity.

There has been considerable interest in stereochemical control in radical additions to acrylamides where chiral amides are employed as auxiliaries.[1] The presence of an α-phenylthio group has a dramatic effect on the stability of a radical formed by conjugate addition to an acrylamide, by the captodative effect.[2] We wish to report a novel, efficient and stereospecific synthesis of α-phenylthio-β-chloro acrylamide derivatives **2** which we have recently developed, illustrated in equation (1). Investigation of the reactivity of these compounds including their behaviour with radicals should prove interesting; research is underway to explore their synthetic utility.



1 **2** (1)

The α-chloro sulfide **3a** was required as an electrophile for a synthetic project under investigation in our laboratory.[3] In attempting to prepare this α-chloro sulfide by treatment of the sulfide **1a** with NCS in carbon tetrachloride the reaction was complicated by unexpected further reaction as illustrated in equation (2).[4] The α-phenylthio-β-chloro acrylamide **2a** and the α-phenylthio acrylamide **4a** were formed in addition to the α-chloro sulfide **3a**, the ratios of the compounds **2a** - **4a** isolated depending strongly on the reaction conditions employed.[5-7]



1a **2a** **3a** **4a** (2)

Conditions for the formation of the α-phenylthio-β-chloro acrylamide **2a** were optimised; thus when **1a** was treated with 2.2 equivalents NCS in refluxing CCl_4 the amide was transformed essentially quantitatively over 18 hours to the α-phenylthio-β-chloro acrylamide **2a**. While the crude product of the reaction was essentially a single compound by ^1H NMR spectroscopy and TLC and was sufficiently pure for use in further reactions, **2a** may be isolated in analytically pure form in 80% yield following trituration with hexane, obviating the necessity for chromatographic purification. Alternatively the analytically pure product could be isolated by recrystallisation from ethanol (59%) or by chromatography on silica (80%).

The serendipitous discovery of this reaction has been exploited in developing a general method for the single step transformation of α-phenylthio secondary amides into the corresponding α-phenylthio-β-chloro acrylamide derivatives as illustrated in the Table, furnishing a remarkably simple one pot route to the *(Z)*-α-phenylthio-β-chloro acrylamides **2**.[5,6,8] This methodology can be employed to synthesise significant quanitities of the *(Z)*-α-phenylthio-β-chloro acrylamides without any difficulty; when 5 g of the amide **1a** was employed, then **2a** was isolated in 74 % yield. Notably this oxidative functionalisation of the amide occurs stereospecifically forming only the *(Z)*-isomer. X-ray analysis[9] of crystals of **2c** established unequivocally the stereochemistry of this acrylamide as shown in Figure 1. The stereochemistry of each of the other acrylamide derivatives was assigned by analogy.

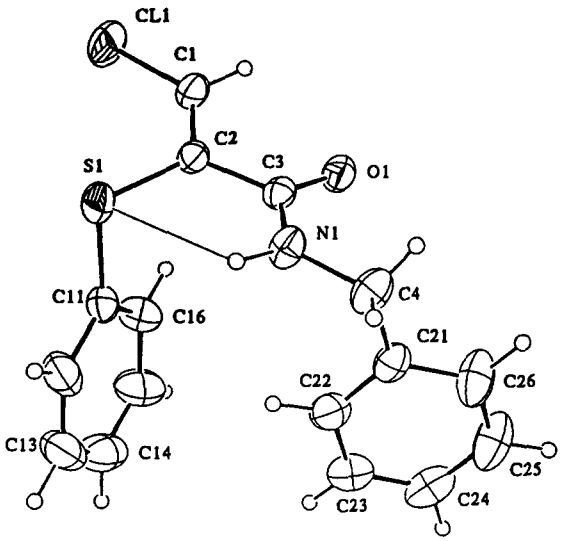


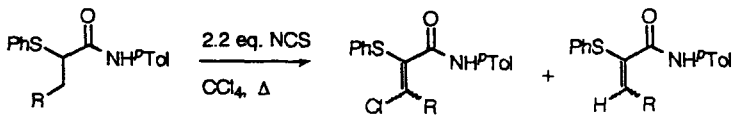
Figure 1 *A view of 2c showing the stereochemistry and the crystallographic numbering scheme. Non-hydrogen atom ellipsoids are at the 30% level; for clarity hydrogen atoms are shown as small spheres of an arbitrary size. The intramolecular N-H...S hydrogen bond 2.59 Å is also shown.*

Table Stereospecific Transformation of α-Phenylthio Secondary Propanamides **1** into the Analogous (*Z*)-α-Phenylthio-β-chloro Propenamide Derivatives **2**

Amide	R^1	Product (Yield %)[a]
1a	^{p}Tol	**2a** (80)
1b	Et	**2b** (63)
1c	CH_2Ph	**2c** (66)
1d	^{i}Pr	**2d** (59)
1e	$CH_2CH{=}CH_2$	**2e** (57) and **4e** (17)

[a]Yield of **2a,b,c,e** isolated following chromatography; the yield reported for **2d** is for the acrylamide purified by recrystallisation from ethanol

As can be seen from the Table the reactions of **1a-d** were very efficient resulting in isolation of the corresponding (*Z*)-α-phenylthio-β-chloro acrylamides **2a-d** as the only identifiable products. However for the *N*-allyl derivative **1e** the transformation was less efficient and the acrylamide **4e** was isolated in addition to the β-chloro derivative **2e**. Furthermore when the reaction of NCS with α-phenylthio amides with extended alkyl chains **1f** and **1g** was attempted some transformation to the α-phenylthio-β-chloro acrylamide derivatives **2f** and **2g** was observed, as a mixture of (*Z*)- and (*E*)-isomers, but the α-phenylthio acrylamides **4f** and **4g** were also isolated in appreciable amounts as illustrated in equation (3). These observations have proved significant in developing a mechanistic rationale for the transformation.[7] While the (*Z*)- and (*E*)-isomers of each of the α-phenylthio-β-chloro acrylamide derivatives **2f** and **2g** were easily separated chromatographically, the α-phenylthio acrylamides **4f** and **4g** were each isolated as an isomeric mixture.



(3)

R		separated isomers		isomeric mixture	
1f	Me	**2f**	19 %, 27 %	**4f**	20 %
1g	Et	**2g**	18 %, 19 %	**4g**	44 %

Typical Experimental

N-4-Methylphenyl (Z)-3-Chloro-2-Phenylthiopropenamide (2a)

A solution of the sulfide **1a** (349 mg, 1.29 mmol) in carbon tetrachloride (10 ml) was stirred at room temperature under nitrogen; NCS (380 mg, 2.85 mmol) was added in one portion. The reaction mixture was stirred at room temperature for 10 min then heated to reflux for 18 h. The reaction mixture was cooled, filtered and concentrated to give the β-chloro acrylamide **2a** as a white solid (399 mg, quantitative). While the crude product is essentially pure by TLC and ^{1}H NMR, an analytically pure sample could be obtained by trituration with hexane (80 %) or recrystallisation from EtOH (59 %): mp 113-4°C; IR (KBr) ν_{max} 3337, 1655, 1592, 1560, 1523, 818 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ_H 8.62 (1H, brs, NH), 8.04 (1H, s, =CHCl), 7.40 - 7.02 (9H, m, Ar-H), 2.28 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ_C 160.27 (CO), 140.72 (CHCl), 134.77, 134.48, 132.52,

130.67 (4 quaternary C), 129.68, 129.52, 128.17, 127.37, 120.21 (5 x CH), 20.90 (CH_3); MS *m/z* 303 ($M^{\cdot+}$, 42), 267 (30), 159 (23), 134 (100), 106 (21), 77 (18). Anal. Calculated for $C_{16}H_{14}ClNOS$: C, 63.26; H, 4.64; Cl, 11.67; N, 4.61; S, 10.55; Found: C, 63.34, H, 4.69; Cl, 11.98; N, 4.34; S, 10.24.

In conclusion, conditions have been discovered for the stereospecific transformation of the α-phenylthio amides **1a-e** to the analogous *(Z)*-α-phenylthio-β-chloro acrylamides **2a-e**. This process may also be applied to synthesis of the substituted acrylamides **2f-g**, albeit less efficiently and without any appreciable stereoselectivity. Further investigation of this transformation, the reactivity of the α-phenylthio-β-chloro acrylamides **2** and their synthetic utility is underway.

Acknowledgements The financial support of the following is gratefully acknowledged: Eolas / Forbairt, University College Cork, especially UCC President's Research Fund, and Ciba (ACE award).

References and Notes

1. Porter, N.A.; Giese, B.; Curran, D.P. *Acc. Chem. Res.*, 1991, **24**, 296.
2. For reviews of the captodative effect see Viehe, H.G.; Merenyi, R.; Stella, L.; Janousek, Z. *Angew. Chem. Int. Ed. Engl.*, 1979, **18**, 917; Viehe, H.G.; Janousek, Z.; Merenyi, R.; Stella, L. *Acc. Chem. Res.*, 1985, **18**, 148; Sustmann, R.; Korth, H.-G. *Adv. Phys. Org. Chem.*, 1990, **26**, 131.
3. (a) For a review of α-chloro sulfides see Dilworth, B.M.; McKervey, M.A. *Tetrahedron*, 1986, **42**, 3731; (b) for an example of their use as electrophiles see Kennedy, M.; McKervey, M.A.; Maguire, A.R.; Naughton, S. *J. Chem. Soc., Perkin Trans. 1*, 1990, 1041; (c) for an example of their use as radical precursors see Ishibashi, H.; Uemura, N.; Nakatani, H.; Okazaki, M.; Sato, T.; Nakamura, N.; Ikeda, M. *J. Org. Chem.*, 1993, **58**, 2360.
4. Preparation of α-chloro-α-arylthio amide derivatives has been reported, *e.g.* Sato, T.; Wada, Y.; Nishimoto, M.; Ishibashi, H.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1*, 1989, 879; Satoh, T.; Kitoh, Y.; Onda, K.; Yamakawa, K. *Tetrahedron Lett.*, 1993, **34**, 2331; see also ref. 3(c) - it may be significant that in this case the secondary amide derivatives were not observed to react in the same way as those of the tertiary amides.
5. All new compounds reported gave satisfactory spectroscopic and analytical data.
6. The amides **1a-e** were prepared by reaction of α-chloropropanoyl chloride with the appropriate amine followed by treatment with sodium thiophenoxide. The amides **1f-g** were prepared in a similar fashion from the appropriate α-halo acid chloride.
7. Investigation of the mechanistic features of these transformations will be discussed elsewhere.
8. α-Phenylthio-β-chloro acrylamide derivatives are mentioned in a patent: Viehe, H.; Van Hoecke, M.; De Mesmaeker, A.; Merenyi R. France Patent No. 2 553 764, 1983.
9. Crystals of **2c** are orthorhombic, space group *Pcab* with 8 molecules of $C_{16}H_{14}ClNOS$ in a unit cell of dimensions a = 9.3100(18), b = 12.3199(14), c = 26.521(3)Å, V = 3040.9(8) $Å^3$, F(000) 1264, μ = 0.38 mm^{-1}. Some 3298 reflections in the θ range 2 - 27° were measured. Of these the 1609 with I > 2.5σ(I) were used in the structure solution and refinement. The structure was solved by direct methods and refined by full-matrix least-squares methods. Final R factors are R = 0.046, wR 0.060. Full details of molecular dimensions, fractional coordinates, thermal parameters and structure factor listing are available from the authors and have been deposited with the Cambridge Crystallographic Data Centre.

(*Received in UK* 24 *October* 1994; *accepted* 18 *November* 1994)