

## THE USE OF $\beta$ -(TRI-N-BUTYLSTANNYL)ACRYLAMIDES AS $\beta$ -LITHIOACRYLAMIDE SYNTHONS

Hussein Imanieh, Donald MacLeod, and Peter Quayle\*

Department of chemistry  
Victoria University of Manchester  
Manchester M13 9PL. UK.

and

Gareth M. Davies  
ICI Pharmaceuticals  
Alderley Park  
Macclesfield SK10 4TG. UK.

*The use of  $\beta$ -(tri-n-butylstannyl)acrylamides as  $\beta$ -lithioacrylamide synthons has been established; such intermediates are potentially versatile synthons for the stereospecific synthesis of tri-substituted double bonds and for the construction of functionalised butenolides.*

The development of  $d^3$  synthons continues to be an area of intense chemical investigation<sup>1</sup> as the synthetic utility of homoenolates<sup>2</sup> and in particular  $\beta$ -acylvinyl anion equivalents<sup>3</sup> becomes more apparent. At present there exist a number of methods in the literature for the preparation of  $\beta$ -acylvinyl anions, the most direct of which being the kinetic deprotonation of a variety of acrylates.<sup>4</sup> However the preparation of  $\beta$ -acylvinyl anions *via* kinetic deprotonation is sometimes complicated by rearrangement of the resultant  $\beta$ -anion to the thermodynamically<sup>5</sup> more stable  $\alpha$ -anion or by unwanted condensation or addition reactions.<sup>6</sup> In certain instances such deprotonation reactions are only possible at low temperatures, producing reactive intermediates of only a limited lifetime. Herein we wish to communicate our initial observations in this area and demonstrate the synthetic potential of  $\beta$ -(tri-n-butylstannyl)acrylamides as a convenient source of stable  $\beta$ -lithioacrylamide anions, which themselves undergo a number of useful alkylation reactions.

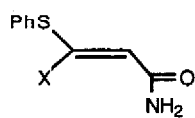
We recently reported<sup>7</sup> that reaction of reactive isocyanates (e.g. CSI and p-toluenesulphonyl isocyanate) with vinyl stannanes resulted in the facile preparation of a variety of  $\beta$ -(tri-n-butylstannyl)acrylamides. Subsequent investigations have established that the acrylamides 1, 6, 21 and 23 undergo clean transmetallation with n-butyl lithium at  $-78^\circ\text{C}$  to afford the tri-anion 4 or the di-anions 8, 25 and 26 respectively. Hence reaction of the acrylamide 1 with n-butyl lithium (3.3-4.0 equivalents) in THF at  $-78^\circ\text{C}$  led, after warming up to  $-10^\circ\text{C}$ , to the generation of the stable tri-anion 4. Quenching of tri-anion 4 ( $\text{NH}_4\text{Cl}$  or  $\text{D}_2\text{O}$  at  $-78^\circ\text{C}$ ) led to the formation of the acrylamides 2 and 3 in high yields (84% and ~ quantitative respectively)

indicating that the tri-anion 4 was both regio- and configurationally stable, presumably due to the formation of a stable chelated intermediate such as 5.<sup>8</sup> Interestingly, reaction of the acrylamide 1 with n-butyl lithium (2.0 equivalents) at -78°C to -10°C followed by an aqueous quench at -78°C resulted in the formation (> 90%, <sup>1</sup>H nmr) of the acrylamide 2, presumably *via* the di-anion 9.<sup>9</sup> Reaction of the tosamide derivatives ( e.g. 6) with n-butyl lithium (2.2 equivalents) at -78°C to -60°C led to the generation of yellow coloured di-anions ( e.g. 8 ), which again appear to be stable entities at -30°C. Quenching of the di-anion 8 with either d<sub>4</sub>-HOAc or NaOAc/HOAc buffer also led to regio- and stereospecific deuteration/protonation to afford the tosamide derivatives 12 and 13 respectively. Similarly, metallation of the stannane 7 and subsequent protonation afforded the acrylamide 14 (40% isolated yield). In addition, generation of the di-anion 26 derived from the stannane 23 as above, afforded, upon protonation, the pyran derivative<sup>10</sup> 24 in 52% isolated yield.

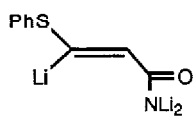
Upon establishing the ability to prepare anions such as 4, we decided to investigate further their alkylation chemistry. Unfortunately attempted alkylation of the tri-anion 4 with methyl iodide at -78°C led to the formation of an inseparable mixture of C- and N- alkylated products. However, monosilylation<sup>11</sup> of 1 afforded the chromatographically stable amides<sup>12</sup> 15 and 16 in 90 and 91% isolated yield, which upon conversion to the di-anions 10 and 11 (2.2 equivalents n-BuLi, -78°C) and subsequent methylation cleanly afforded the C-methylated products 17, 19 (17:19=1:2.7; partial de-silylation occurred *in situ*) and 18 in good overall yield( 70% and 63% respectively). In order to establish the stereochemical course of this reaction, oxidation of the amide 19 was undertaken. Hence, reaction of the amide 19 with MCPBA (1 equivalent) at ambient temperature afforded the sulphoxide 20 in 51% unoptimised yield, in which H<sup>a</sup> had experienced a downfield shift from 5.20 to 7.10 ppm, inferring a *cis* relationship between the sulphur residue at C-3 and H<sup>a</sup>.

The synthesis of butenolides<sup>13</sup> and related compounds<sup>14</sup> has been the subject of much recent investigation. We considered that reaction of a d<sup>3</sup> synthon e.g. 4 with an aldehyde or ketone and subsequent cyclisation could provide a concise approach<sup>15</sup> to this important class of compounds<sup>12</sup>. Hence reaction of the tri-anion 4 with benzophenone and acidification led to the isolation of the hydroxy-amide 27 in 63% yield. Alternatively, if work-up was delayed (i.e. allowed to stir at 25°C overnight) after the acid quench, direct cyclisation to the butenolide 28 was observed in 67% overall yield in a "one-pot" procedure. In an analogous fashion, reaction of the furan carboxaldehyde 29 with the tri-anion 4 afforded the hydroxy-amide 30 (64%), which could be cyclised to the butenolide 31 in quantitative yield upon exposure to activated silica in dry THF. Whereas reaction of the tri-anion 4 with benzaldehyde cleanly afforded the hydroxy-amide 32 (61%), reaction with butanal under similar conditions afforded the product 33 in only meagre yield (23%). Current work is in hand in order to improve the reaction of the tri-anion 4 with potentially enolizable substrates. Encouragingly however, reaction of the di-anion 8 with decan-4-one at -78°C and allowing the reaction mixture to warm up to room temperature resulted in the direct conversion to the butenolide 34 in 80% yield.

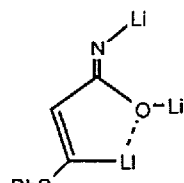
In a similar fashion, reaction of the di-anion 8 with benzophenone at -78°C followed by allowing the reaction mixture to warm up to room temperature led to the direct formation of



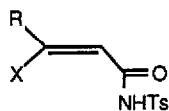
- X = SnBu<sub>3</sub> (1)  
 X = H (2)  
 X = D (3)



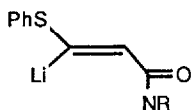
(4)



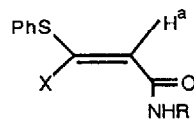
(5)



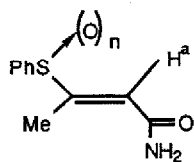
- R = SPh; X = SnBu<sub>3</sub> (6)  
 R = OEt; X = SnBu<sub>3</sub> (7)  
 R = SPh; X = H (12)  
 R = SPh; X = D (13)  
 R = OEt; X = H (14)



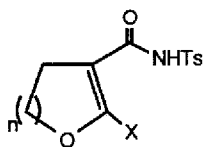
- R = Ts; (8)  
 R = H; (9)  
 R = TBDMS; (10)  
 R = TIPS; (11)



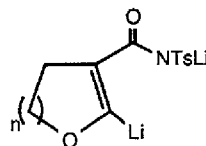
- R = TBDMS; X = SnBu<sub>3</sub>; (15)  
 R = TIPS; X = SnBu<sub>3</sub>; (16)  
 R = TBDMS; X = Me; (17)  
 R = TIPS; X = Me; (18)



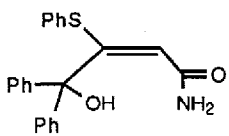
- n = 0; (19)  
 n = 1; (20)



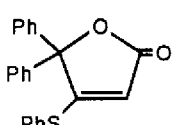
- n = 1; X = SnBu<sub>3</sub>; (21)  
 n = 1; X = H; (22)  
 n = 2; X = SnBu<sub>3</sub>; (23)  
 n = 2; X = H; (24)



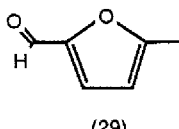
- n = 1; (25)  
 n = 2; (26)



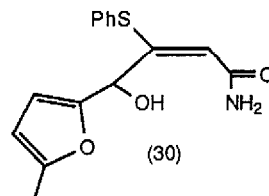
(27)



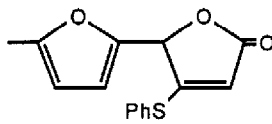
(28)



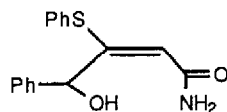
(29)



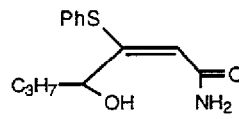
(30)



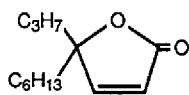
(31)



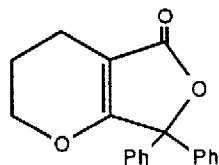
(32)



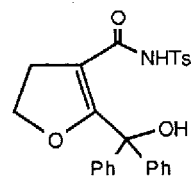
(33)



(34)



(35)



(36)

the butenolide 28 in 87% isolated yield. Whereas capture of the furan-derived carbanion 25 with benzophenone afforded the amide 36 (40%), reaction of the carbanion 26 resulted in the direct conversion to the bi-cyclic system 35 (52%).

Further applications of tin acrylamides such as 21 and 23 in natural product synthesis are currently under investigation, and the results of these studies will be reported elsewhere.<sup>16</sup>

#### Acknowledgements.

One of us (D.M.) thanks the SERC for the provision of a CASE award; we thank ICI pharmaceuticals for generous support of our work.

#### References and notes.

- (1) D. Seebach, Angew. Chem., Int. Edn. Engl., 1979, 18, 239; J. C. Stowell, Chem. Rev., 1984, 84, 409; "Unpoled Synthons", T. A. Hase (ed), John Wiley, 1987 J. Barluenya, J. R. Fernandez, C. Rubiera, and M. Yus, J. Chem. Soc., Perkin Trans. I, 1988, 3113 and refs. therein.
- (2) D. J. Kryson and P. B. MacKenzie, J. Amer. Chem. Soc., 1988, 110, 6270; Y. Tamura, H. Ochai, T. Nakamura, and Z.-i Yoshida, Angew. Chem., Int. Edn. Engl., 1987, 26, 1157; I. Kuwajima, Pure and Applied Chemistry, 1988, 60, 115; S. Aoki, T. Fujimara, E. Nakamura, and I. Kuwajima, J. Amer. Chem. Soc., 1988, 110, 3296, Tetrahedron Letters, 1988, 29, 1541; for a review article see N. H. Werstuijk, Tetrahedron, 1983, 39, 205.
- (3) e.g. C. Najera and M. Yus, J. Org. Chem., 1988, 53, 4708.
- (4) K. Isobe, M. Fuse, H. Kosugi, H. Hagiwara and H. Uda, Chem. Letters, 1979, 785; Y. Takahasi, H. Hagiwara, H. Uda and H. Kosugi, Heterocycles, 1981, 15, 225; R. R. Schmidt, Tetrahedron, 1983, 39, 2043; R. R. Schmidt and R. Hirsenkorn, Tetrahedron Letters, 1984, 25, 4357; N. C. Barau and R. Schmidt, Chem. Ber., 1986, 119, 2066; R. R. Schmidt, A. Enhsen, and R. Betz, Synthesis, 1985, 160.
- (5) R. R. Schmidt, J. Talbiersky and P. Russeger, Angew. Chem., Int. Edn. Engl., 1977, 16, 853, Tetrahedron Letters, 1979, 4273;
- (6) R. R. Schmidt and J. Talbiersky, Angew. Chem., Int. Edn. Engl., 1976, 15, 171.
- (7) H. Imanieh, D. MacLeod, P. Quayle, and G. M. Davies, Tetrahedron Letters, submitted for publication.
- (8) c.f. W. R. Baker and R. M. Coates, J. Org. Chem., 1979, 44, 1022.
- (9) For related examples see P. Beak and A. I. Meyers, Acct. Chem. Res. 1986, 19, 356; normally deprotonation of relatively acidic hydrogens occurs prior to tin-lithium exchange e.g. N. Meyer and D. Seebach, Chem. Ber., 1980, 113, 1290; R. H. Newman-Evans and B. K. Carpenter, Tetrahedron Letters, 1985, 26, 1141.
- (10) F. Effenberger and R. Gleiter, Chem. Ber., 1964, 97, 1576
- (11) The di-anion of N-(trimethylsilyl)acetamide undergoes clean C-alkylation reactions, c.f. P. C. Kuzma, L. E. Brown, and T. M. Harris, J. Org. Chem., 1984, 49, 2015. Attempted N-trimethylsilylation of the amide 1 afforded a highly labile intermediate which could not be purified.
- (12) The silylated amides 15 and 16 were most conveniently prepared by deprotonation of the amide 1 (n-BuLi; 1 eq., -78°C to 0°C) followed by reaction with either TBDMSCl or TIPSCl in THF overnight at ambient temperature. Removal of the solvent *in vacuo* and subsequent "flash chromatography" afforded the protected amides in excellent yield.
- (13) Y. S. Rao, Chem. Rev., 1976, 76, 625
- (14) e.g. M. S. Chambers and E. J. Thomas, J. Chem. Soc., Chem. Commun., 1989, 23; A. F. Thomas and Y. Bessiere in "Total Synthesis of Natural Products", Vol. 6. J. ApSimon (ed.), John Wiley, 1988.
- (15) c.f. R. R. Schmidt and R. Betz, Angew. Chem., Int. Edn. Engl., 1984, 23, 430 and refs therein.
- (16) H. Imanieh, D. Macleod, P. Quayle and G. M. Davies, unpublished results.

(Received in UK 4 April 1989)