Tetrahedron Letters, Vol. 33, No. 7, pp. 935-938, 1992
Printed in Great Britain

0040-4039/92 $3.00 + .00
Pergamon Press plc

Mono S-trimethylsilyl ketene dithioacetals as versatile tools for the synthesis of α-hydrazinodithioesters. A novel access to endothiopeptides.

Pierre Beslin* and Philippe Marion.

Laboratoire de Chimie des Composés Thioorganiques (Associé au CNRS) ISMRA, Université de Caen , 6, Boulevard Maréchal Juin, 14050 Caen, France.

Abstract: Mono-S-trimethylsilylketene dithioacetals have been prepared from dithioesters by the action of trimethylsilyl iodide formed in situ. They were reacted easily with dialkylazodicarboxylates to give good yields of α-hydrazinodithioesters. The latter were transformed into thioamides or endothiodipeptides by aminolysis either with an amine or an amino acid.

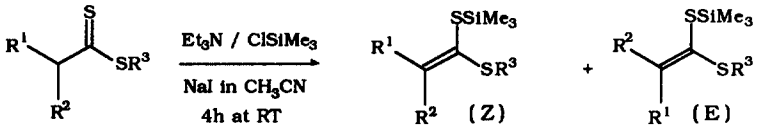
Metal thioenolates of dithioesters are versatile tools for the stereocontrolled formation of carbon-carbon bonds.[1-7] Their trialkylsilyl equivalents, the mono S-trimethylsilyl ketene dithioacetals, although well-known[8-10], have been scarcely used in organic synthesis.[9-10]

In connection with our continuous efforts to extend the sulfur chemistry area, we decided to develop the chemistry of these trialkylsilyl intermediates. As already reported, they react easily with aldehydes[9-10] and, in our hands, acceptable stereochemical control has been observed.[11]

In this paper, we disclose our first results concerning a new route to mono S-trialkylsilylketene dithioacetals and their condensation with nitrogen electrophiles like the dialkylazodicarboxylates. It will thus open an access to unreported α-hydrazinodithioesters, which may be potential residues of endothiopeptides, with the assumption that they will exhibit some specific biological activity as do their oxygenated counterparts.[12] Our strategy differs from the classic synthesis of α-amino substituted dithioesters, thioamides or thiopeptides derived from N-protected aminoacids.[13-15]

Mono S-trimethylsilylketene dithioacetals are generally prepared from dithioesters either by LDA promoted deprotonation followed by in situ S-silylation with trimethylsilyl

chloride[8] or by using trimethylsilyl triflate in the presence of triethylamine.[10] We succeeded in such a synthesis using Duboudin's proposed method for the preparation of enoxysilanes from ketonic compounds.[16] Thus the combined action of triethylamine and trimethylsilyl iodide formed *in-situ* from trimethylsilyl chloride and sodium iodide, afforded mono S-trimethylsilyl ketene dithioacetals in good yields from several dithioesters (see scheme I and table I). Isolation procedure consists of a simple filtration under nitrogen atmosphere and solvent evaporation.

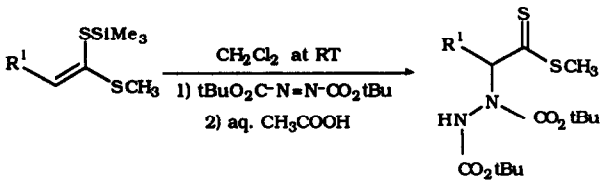


Scheme I

Table I

Entry	R^1	R^2	R^3	Yield (%)	Z/E ratio	Z/E ratio with LDA
1	Me	H	Me	86	72/28	75/25
2	Me	Me	Me	73	-	-
3	Ph	H	Me	80	70/30	-
4	$PhCH_2$	H	Me	86	92/08	-
5	H	H	Me	75	-	-
6	nC_5H_{11}	H	Me	84	82/18	85/15
7	nC_8H_{17}	H	Me	75	60/40	-
8	Me	H	tBu	71	88/12	84/16
9	Me	H	Et	80	84/16	70/30
10	Me	H	CH_2Ph	81	70/30	84/16
11	$-(CH_2)_4-$		Me	85	-	-
12	$-(CH_2)_5-$		Me	88	-	-

The Z/E ratios reported in table I were determined by ^1H NMR or VPC. They are very similar to the Z/E ratios of the S-alkyl diastereoisomer analogs (see the last column in table I) formed by the LDA procedure whose Z selectivity has been proven.[6-7]



Scheme II

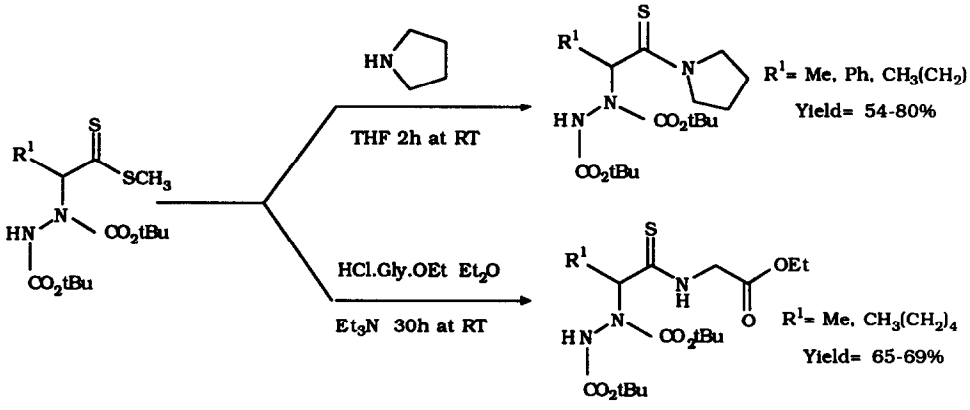
Mono S-trimethylsilyl ketene dithioacetals reacted more readily than the corresponding ketene acetals with dialkyl azidodicarboxylate.[17-19] The condensation occured at room temperature without the help of any catalyst. After quenching with diluted acetic acid and the usual work-up followed by flash chromatography, in all runs except run 6, N,N'-di-Boc-α-hydrazinodithioesters were isolated with a good yield (see scheme II and Table II).

Table II

Entry	R^1	Reaction time (h)	Yield (%)
1	Me	1	72
2	nC_5H_{11}	1	75
3	nC_8H_{17}	1	80
4	Ph	2	69
5	$PhCH_2$	1	76
6	H	3	37
7	$(CH_3)_2$	3	90

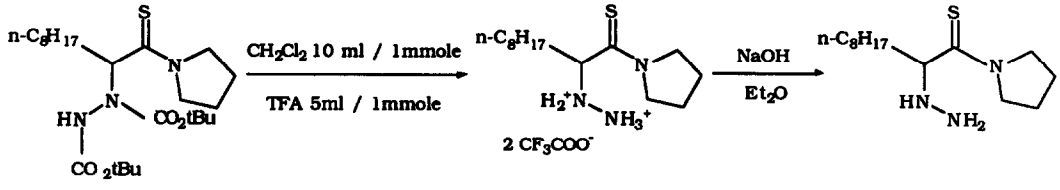
With the aim of using such compounds as a residue for endothiopeptide synthesis, deprotection of N,N'-di-Boc-α-hydrazinodithioesters (R^1= Me, $CH_3(CH_2)_7$, H) was attempted but failed in all conditions.[20]

So, as the next step will be an aminolysis reaction of dithioester functionality, we successfully transformed the N,N'-di-Boc-α-hydrazinodithioesters into thioamides either by the action of a simple amine such as pyrrolidine or by that of ethyl glycinate hydrochloride in the presence of triethylamine (see scheme III).



Scheme III

Some model cleavage reactions have been realized successfully with pyrrolidino N,N'-di-Boc-α-hydrazinothioamide (scheme IV) and we are now testing the same deprotection of the above protected endothiopeptide, BocNHN(Boc)-C(R)-C(=S)-GlyOEt, keeping in mind a future coupling of this deprotected endothiopeptide with various aminoacids either at Nα or Nβ of the hydrazino moiety.[21-22]



Scheme IV

References

1. Beslin P., Perrio S., *Tetrahedron*, 1991, **47**, 6275-6285.
2. Berrada S., Desert S., Metzner P., *Tetrahedron*, 1988, **44**, 3575-3586.
3. Metzner P., *Phosphorus, Sulfur and Silicon*, 1991, **52**, 1-16.
4. Meyers A.I., Tait T.A., Commins D.L., *Tetrahedron Lett.*, 1978, **47**, 4657-4660. Meyers A.I., Babiak K.A., Campbell A.L., Commins D.L., Flemming M.P., Henning. R., Heuschmann M., Hudspeth J.P., Kane J.M., Reider P.J., Roland D.M., Shimizu K., Tomioka K., Walkup R.D., *J. Am. Chem. Soc.*, 1983, 5051-5024.
5. Lawson K.R., Singleton A., Whitham G.H., *J. Chem. Soc. Perkin Trans. I*, 1984, 859-864.
6. Beslin P., Vallée Y., *Tetrahedron*, 1985, **41**, 2691-2705.
7. Berrada S., Metzner P., Rakotonirina R., *Bull. Soc. Chim. Fr.*, 1985, 881-890. Kpegba K., Metzner P., Rakotonirina R., *Tetrahedron Lett*, 1986, **27**, 1505-1508; *Tetrahedron*, 1989, **45**, 2041-2056.
8. Sukhai R., Brandsma L., *Synthesis*, 1979, 455-457.
9. Iwasawa N., Yura T., Mukaiyama T., *Tetrahedron*, 1989, **45**, 1197-1207.
10. Hartke K., Kunze O., *Liebigs Ann. Chem.*, 1989, 321-330.
11. Beslin P., Marion P. unpublished results.
12. Spatola A.F. in *'Chemistry and Biochemistry of Amino Acids, Peptides and Proteins '* (Ed. B. Weinstein), Dekker, 1983, Vol. 7, pp 267-357.
13. Brown D.W., Campbell M.M., Walker C.V., *Tetrahedron*, 1983, **33**, 1075-1083.
14. Jensen O.E., Senning A., *Tetrahedron*, 1986, **42**, 6555-6564.
15. Clausen K., Thorsen M., Lawesson S.O., *J. Chem. Soc. Perkin Trans. I*, 1984, 785-798 and cited refs.
16. Cazeau P., Moulines F., Laporte P., Duboudin F., *J. Organomet. Chem.*, 1980, **201**, C9-C13. Cazeau P., Duboudin F., Moulines F., Babot O., Dunogues J., *Tetrahedron*, 1987, **43**, 2075-2088. Cazeau P., Duboudin F., Moulines F., Babot O., Dunogues J., *Tetrahedron*, 1987, **43**, 2089-2100. Rochin C., Babot O., Dunogues J., Duboudin F., *Synthesis*, 1986, 667-668.
17. Evans D.A., Britton T.C., Dorow R.L., Dellaria Jr. J.F., *Tetrahedron*, 1988, **44**, 5525-5540.
18. Gennari C., Colombo L., Bertolini G., *J. Am. Chem. Soc.*, 1986, **108**, 6394-6395.
19. Oppolzer W., Moretti R., *Helv. Chim. Acta*, 1986, **69**, 1923-1926. Oppolzer W., Moretti R., *Tetrahedron*, 1988, **44**, 5541-5552.
20 Scarpino L.A., *Acc. Chem. Research*, 1973, **6**, 191-198.
21. Lecocq A., Marraud M., *Tetrahedron Lett.*, 1991, **32**, 2765-2768.
22. Viret J., Collet A., *New J. Chem.*, 1988, **12**, 253-256.

(Received in France 5 November 1991)