

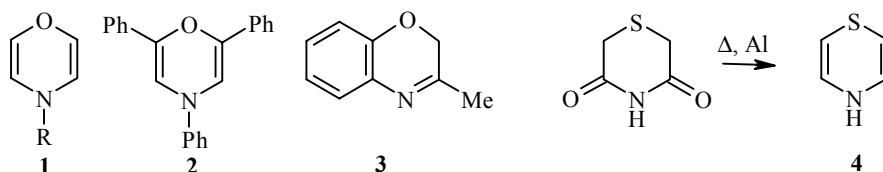
SYNTHESIS AND PYROLYSIS OF TETRAHYDRO-1,4-OXAZINE- 3,5-DIONES AND TETRAHYDRO- 1,4-THIAZINE-3,5-DIONES*

R. A. Aitken, D. M. M. Farrell, and E. H. M. Kirton

The preparation and characterization of six 4-substituted tetrahydro-1,4-oxazine-3,5-diones and five 4-substituted tetrahydro-1,4-thiazine-3,5-diones is described. Upon flash vacuum pyrolysis at 700°C these give *N*-substituted acetamides and nitriles, and a mechanism for formation of these products is proposed.

Keywords: acetamides, diradicals, nitriles, tetrahydrooxazinediones, pyrolysis.

For some time we have been interested in preparing simple monocyclic 1,4-oxazines **1**. The simplest example prepared to date appears to be the 2,4,6-triphenyl compound **2** [1], and a number of fused derivatives such as **3** are also known [2]. In contrast to this situation, the parent 1,4-thiazine **4** was prepared as early as 1948 by gas-phase deoxygenation of the cyclic imide of thiodiglycolic acid over aluminum [3].

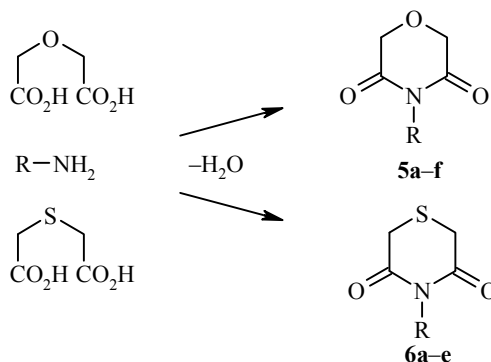


Since we have previously found that flash vacuum pyrolysis (FVP) over magnesium is effective in dehalogenation and also deoxygenation of a wide variety of organic substrates [4], we were interested to examine this method as an approach to synthesis of simple 1,4-oxazines. We describe here the synthesis and spectroscopic characterization of a range of *N*-substituted tetrahydro-1,4-oxazine-3,5-diones **5** and the related tetrahydro-1,4-thiazine-3,5-diones **6** and the first study of their pyrolysis under FVP conditions, which takes an unexpected course.

An important but little known early paper describes the preparation of a variety of *N*-substituted tetrahydro-1,4-oxazine-3,5-diones **5** by condensation of diglycolic acid with amines and their evaluation as sweetening agents in analogy to saccharin [5]. The six compounds **5a-f** were readily prepared by heating a mixture of the appropriate amine with diglycolic acid with removal of the water formed by distillation followed

* Dedicated to Professor Edmunds Lukevics on the occasion of his 65th birthday.

by Kugelrohr distillation of the products under reduced pressure. The five tetrahydrothiazinediones **6a-e** were similarly prepared starting from thiodiglycolic acid. The compounds gave satisfactory analytical and spectroscopic data including a highly consistent pattern in the ^1H and ^{13}C NMR spectra (Table 1). Due to their early date of preparation, spectroscopic data appear not to have been previously reported for any of these compounds with the exception of **5a** and **6a** for which ^1H NMR data have appeared [6] and are in good agreement with those presented here.

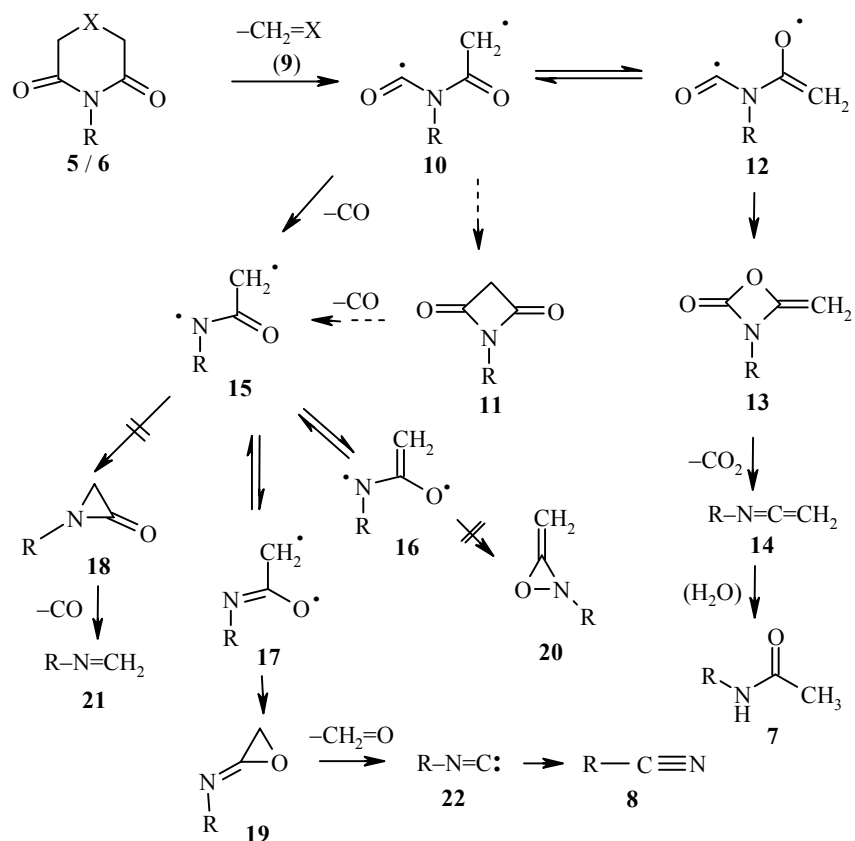


When selected examples of the heterocyclic compounds were subjected to FVP at 700°C they produced rather complex mixtures of products which were difficult to identify directly. For this reason the product mixtures were subjected to preparative TLC on silica and this led to identification of the N-substituted acetamides **7** and the nitriles **8** in all the five cases examined. The yields of each of these products estimated from calibration of GC-MS and ^1H NMR spectra were in the range of 20-30%. The rather complex nature of the crude product mixtures coupled with the need for careful separation led to significant loss of products. The formation of these products is rather interesting and in Scheme 1 we propose a mechanism by which they might be formed. The first point to note is that the only 1,4-thiazine compound examined, **6c**, gave exactly the same products as the corresponding 1,4-oxazine **5c**. This suggests early loss of the X atom and we propose that this is in the form of (thio)formaldehyde **9**. This is consistent with the mass spectrum of **5f** where there is initial loss of CH₂O. The resulting diradical **10** may either ring-close directly to give the azetidinedione **11**, or isomerize to **12** which can ring-close to give the oxazetidione **13**. This would be expected to easily extrude CO₂ under the conditions and thus afford the ketenimines **14**. Although compounds of this type were first prepared in the 1920's [7] they are known to be prone to polymerization and would certainly be expected to undergo hydration to the acetamides **7** upon chromatography on silica. These facts agree with our observations since the acetamides **7** were not present in the crude pyrolysis products but were only formed during the chromatographic purification. Careful examination of the spectra of the crude products did not reveal any signals corresponding to the ketenimines **14** although the spectroscopic data of **14b-d** were available for comparison [8-11].

The other products, the nitriles **8**, obviously require loss of all oxygen and we believe that their formation involves the intermediate diradicals **15**. These may either be formed by extrusion of CO from **11** or, perhaps more likely, directly from the diradicals **10**. As shown the C,N-diradical species **15** has a number of pathways to open since it can also exist in the N,O-form **16** or the C,O-form **17**. A detailed theoretical study on the parent system (R = H) [12] predicts that ring-closure of these species to give **18** is most favorable with **19** higher in energy by 30.8 or 26.0 kJ mol⁻¹ (depending on whether the R group is *E* or *Z*) while **20** has a very high energy (195.6 kJ mol⁻¹). We take this last fact, coupled with the lack of any obvious further breakdown pathway for **20**, to mean that it is unlikely to be involved here. The apparent non-involvement of **18** is harder to explain since it is predicted to be more stable than **19** but this is, in fact, in agreement with previous studies on pyrolysis of isolated aziridinones [13], where nitriles and carbonyl compounds were generally produced by way of the isomerization corresponding to **18-15-17-19**. No trace of the imines **21** expected from extrusion of CO from **18**

was observed in any of the spectra of the crude pyrolysis products despite data for these compounds being available for comparison [14, 15]. The nitriles are thus likely to be formed as shown by ring-closure of the diradical **17** to give the iminoxiranes **19** which extrude formaldehyde to give the isonitriles **22** and these isomerize to the more stable nitriles under the conditions involved.

Scheme 1



The pathway proposed here is similar to our recent findings [16] on oxazolidine-2,4-diones **23** which were found to fragment under similar conditions by loss of CO_2 . In this case with a phenyl group on the ring, the position of equilibrium between **24** and **25** seems to be different since products **26** and **27/8** are formed in approximately equal amounts.

Although the gas-phase reaction described here is clearly of no synthetic value, it has allowed new insight into the behavior of some interesting reactive intermediates not readily accessible by other means.

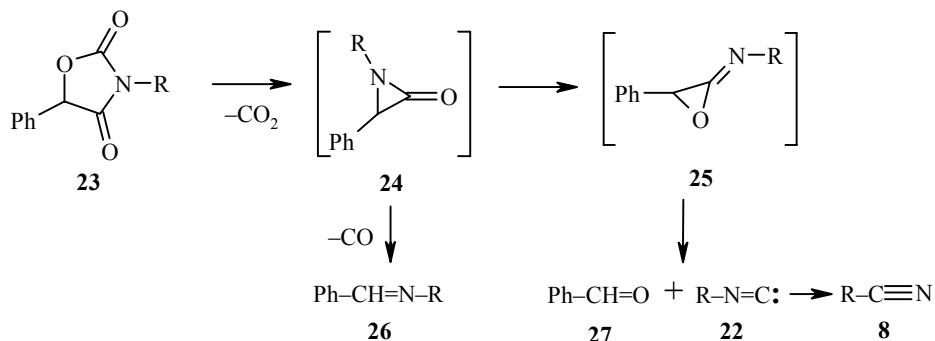


TABLE 1. NMR Spectroscopic Data for 4-Substituted Tetrahydro-1,4-oxa(thia)zine-3,5-diones **5** and **6**

Compound	X	R	¹ H NMR signals, δ		¹³ C NMR signals, δ		
			CH ₂ *	R* ²	CH ₂	CO	R
5a	O	H	4.20	—	66.6	171.5	—
5b	O	Ph	4.55	7.55-7.45 (3H, m), 7.30-7.20 (2H, m)	67.6	170.1	133.6 (<i>ipso</i> -C), 129.2 (2C), 129.0 (2C), 128.8
5c	O	Me	4.40	3.00 (3H, s)	67.1	170.2	24.8
5d	O	Et	4.40	3.66 (2H, q), 1.04 (3H, t)	67.3	170.1	32.2, 13.0
5e	O	Bn	4.40	7.29 (5H, m), 4.92 (2H, s)	68.1	168.2	136.6 (<i>ipso</i> -C), 129.4 (2C), 129.0 (2C), 128.4, 42.4
5f	O	Bu	4.40	3.65 (2H, t), 1.45 (2H, m), 1.27 (2H, m), 0.89 (3H, t)	67.1	170.2	37.6, 29.6, 19.7, 13.7
6a	S	H	3.50	—	30.3	170.5	—
6b	S	Ph	3.85	7.50-7.40 (3H, m), 7.15-7.05 (2H, m)	31.7	169.7	136.1 (<i>ipso</i> -C), 129.1(2C), 128.8 (2C), 128.3
6c	S	Me	3.71	3.07 (3H, s)	31.3	169.7	27.1
6d	S	Et	3.70	3.72 (2H, q)	31.4	171.2	35.2, 13.2
6e	S	Bn	3.56	7.4-7.25 (5H, m), 4.98 (2H, s)	32.4	168.4	136.6 (<i>ipso</i> -C), 128.5 2C), 128.4 (2C), 127.5, 43.7

* All (4 H, s).

*² All coupling constants 7 Hz.

EXPERIMENTAL

Melting points were recorded on a Reichert hot-stage microscope and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1420 instrument. NMR spectra were obtained for ¹H at 300 MHz and for ¹³C at 75 MHz using a Bruker AM300 instrument. Spectra were run on solutions in CD₃SOCD₃ (compounds **5** and **6**) or CDCl₃ (FVP products) with internal Me₄Si as reference. Chemical shifts are reported in ppm to high frequency of the reference and coupling constants *J* are in Hz. Mass spectra were obtained on an AEI/Kratos MS-50 spectrometer using electron impact at 70 eV.

Synthesis of Tetrahydro-1,4-oxazine-3,5-diones and Tetrahydro-1,4-thiazine-3,5-diones. General Procedure. One equivalent of the appropriate amine, either neat or as an aqueous solution, was added cautiously to (thio)diglycolic acid in a flask set up for distillation. The mixture was slowly heated and water distilled off first under atmospheric pressure and then at 20 Torr. The residue was then subjected to Kugelrohr distillation at 0.1 Torr to give the crude product which was recrystallized as noted to give the pure product. For the ¹H and ¹³C NMR spectra of compound **5a-f** and **6a-e**, see Table 1.

Tetrahydro-1,4-oxazine-3,5-dione (5a). Reaction using diglycolic acid (13.4 g, 100 mmol) and aqueous ammonia (*d* 0.88, 15 cm³) gave the product (9.75 g, 85%) as colorless crystals which did not require recrystallization; mp 138-140°C (lit. mp 142°C [5]); IR (nujol), ν, cm⁻¹: 3400, 1732, 1272, 1222, 1123, 1072, 956, 877, 832.

4-Phenyltetrahydro-1,4-oxazine-3,5-dione (5b). Reaction using diglycolic acid (6.7 g, 50 mmol) and aniline (5.12 g, 55 mmol) yielded the product (6.77 g, 71%) as colorless crystals from CH₂Cl₂; mp 194-196°C (lit. mp 195°C [5]). IR (nujol), ν, cm⁻¹: 1743, 1688; *m/z* 191 (M⁺, 97%), 119 (11), 105 (100), 93 (17), 77 (22).

4-Methyltetrahydro-1,4-oxazine-3,5-dione (5c). Reaction using diglycolic acid (6.7 g, 50 mmol) and a 40% solution of methylamine (4.2 g, 54 mmol) yielded the product (5.14 g, 80%) as colorless crystals which did not require recrystallization; mp 72-74°C (lit. mp 78°C [5]); IR (nujol), ν , cm^{-1} : 1732; m/z 129 (M^+ , 95%), 100 (12), 71 (7), 44 (96), 42 (100).

4-Ethyltetrahydro-1,4-oxazine-3,5-dione (5d). Reaction using diglycolic acid (6.7 g, 50 mmol) and a 70% solution of ethylamine (3.54 g, 55 mmol) yielded the product (3.77 g, 53%) as colorless crystals from acetonitrile; mp 29-30°C (lit. bp 95°C/15 Torr [5]). (Found, %: C 50.56; H 6.43; N 9.80. $\text{C}_6\text{H}_9\text{NO}_3$. Calculated, %: C 50.34; H 6.34; N 9.78). IR (thin film), ν , cm^{-1} : 1742, 1685; m/z 143 (M^+ , 100%), 115 (15), 85 (75), 56 (13), 42 (65).

4-Benzyltetrahydro-1,4-oxazine-3,5-dione (5e). Reaction using diglycolic acid (6.7 g, 50 mmol) and benzylamine (5.4 g, 50 mmol) yielded the product (6.1 g, 60%) as colorless crystals which did not require recrystallization; mp 46-48°C (Found: m/z 205.0731 [M^+]. $\text{C}_{11}\text{H}_{11}\text{NO}_3$. Calculated: $M = 205.0739$); IR (melt), ν , cm^{-1} : 1780, 1740, 1682; m/z 205 (M^+ , 100%), 146 (60), 118 (22), 104 (40), 91 (51).

4-Butyltetrahydro-1,4-oxazine-3,5-dione (5f). Reaction using diglycolic acid (6.7 g, 50 mmol) and butylamine (5.11 g, 70 mmol) yielded the product (5.83 g, 68%) as colorless crystals from acetonitrile; mp 26.5-27.5°C (lit. bp 139°C/16 Torr [5]). (Found: m/z 171.0891 [M^+]. $\text{C}_8\text{H}_{13}\text{NO}_3$. Calculated: $M = 171.0895$); IR (thin film), ν , cm^{-1} : 1750, 1670; m/z 171 (M^+ , 10%), 141 (56), 129 (10), 116 (70), 88 (40), 85 (52), 42 (100).

Tetrahydro-1,4-thiazine-3,5-dione (6a). Reaction using thiodiglycolic acid (15 g, 100 mmol) and aqueous ammonia (d 0.88, 15 cm^3) gave the product (9.3 g, 71%) as colorless crystals which did not require recrystallization; mp 118-120°C (lit. mp 128°C [3]); IR (nujol), ν , cm^{-1} : 3420, 1728, 1270, 1194, 1143, 918, 856, 790, 657.

4-Phenyltetrahydro-1,4-thiazine-3,5-dione (6b). Reaction using thiodiglycolic acid (4.6 g, 31 mmol) and aniline (3.3 g, 35 mmol) with the normal procedure gave a solid after Kugelrohr distillation which consisted partly of the non-cyclized thiodiglycolic acid monoanilide. This was heated with acetyl chloride (5 cm^3) and distilled until no more liquid came off. The residual solid was then Kugelrohr distilled to give the final product (1.96 g, 31%) as pale orange crystals from acetonitrile; mp 214.5-215.5°C. Found, %: C 58.09; H 4.55; N 6.75. $\text{C}_{10}\text{H}_9\text{NO}_2\text{S}$. Calculated, %: C 57.95; H 4.38; N 6.76. IR (nujol), ν , cm^{-1} : 1720, 1676; m/z 207 (M^+ , 100%), 179 (17), 135 (8), 117 (27), 106 (18), 93 (19), 77 (17).

4-Methyltetrahydro-1,4-thiazine-3,5-dione (6c). Reaction using thiodiglycolic acid (7.5 g, 50 mmol) and a 40% solution of methylamine (4.26 g, 55 mmol) yielded the product (3.72 g, 51%) as yellow crystals which did not require recrystallization; mp 52-53°C. Found: m/z 145.0202 [M^+]. $\text{C}_5\text{H}_7\text{NO}_2\text{S}$. Calculated: $M = 145.0197$. IR (melt), ν , cm^{-1} : 1686; m/z 145 (M^+ , 100%), 88 (19), 84 (7), 60 (73).

4-Ethyltetrahydro-1,4-thiazine-3,5-dione (6d). Reaction using thiodiglycolic acid (7.5 g, 50 mmol) and a 70% solution of ethylamine (3.2 g, 50 mmol) yielded the product (3.85 g, 45%) as pale brown oily crystals from acetonitrile; mp 29-31°C. Found: m/z 159.0350 [M^+]. $\text{C}_6\text{H}_9\text{NO}_2\text{S}$. Calculated: $M = 159.0354$. IR (thin film), ν , cm^{-1} : 1720, 1665; m/z 159 (M^+ , 9%), 132 (28), 104 (20), 87 (100), 60 (55).

4-Benzyltetrahydro-1,4-thiazine-3,5-dione (6e). Reaction using thiodiglycolic acid (7.5 g, 50 mmol) and benzylamine (5.4 g, 50 mmol) yielded the product (8.2 g, 74%) as a colorless viscous liquid (Found: m/z 221.0504 [M^+]. $\text{C}_{11}\text{H}_{11}\text{NO}_2\text{S}$. Calculated: $M = 221.0511$); IR (thin film), ν , cm^{-1} : 1750, 1700; m/z 221 (M^+ , 100%), 179 (16), 146 (45), 132 (76), 104 (40), 91 (85).

Flash Vacuum Pyrolysis of Tetrahydro-1,4-oxa(thia)zine-3,5-diones. General Procedure. The sample was volatilized from a tube in a Büchi Kugelrohr oven through a 30 × 2.5 cm horizontal fused quartz tube. This was heated externally by a Carbolite Eurotherm tube furnace MTF-12/38A at a temperature of 700°C, the temperature being monitored by a Pt / Pt-13%Rh thermocouple situated at the center of the furnace. The products were collected in a U-shaped trap cooled in liquid nitrogen. The whole system was maintained at a pressure of 10⁻² Torr by an Edwards Model E2M5 high capacity rotary oil pump, the pressure being measured by a Pirani gauge situated between the cold trap and the pump. Under these conditions the contact time in the hot zone was estimated to be ~10 ms.

After the pyrolysis, the system was opened to the air and the products removed for analysis. In this study all products were identified by comparison of GC-MS and NMR data with authentic samples and/or literature values.

FVP of 5b (0.36 g) gave a yellow liquid which was subjected to preparative TLC (SiO₂/Et₂O) to give two major fractions identified as acetanilide **7b** [¹H NMR: 7.60 (2H, d, *J* = 6 Hz), 7.29 (2H, t, *J* = 6 Hz), 7.02 (1H, t, *J* = 6 Hz), 2.07 (3H, s); *m/z* 135 (M⁺, 17%), 93 (100), 43 (38)] and benzonitrile **8b** [¹H NMR: 7.65-7.55 (3H, m), 7.48 (2H, t, *J* = 7 Hz); ¹³C NMR: 132.7, 132.1 (2 C), 129.1 (2 C), 118.8 (*ipso*-C), 112.4 (CN); *m/z* 103 (M⁺, 100%), 76 (50), 50 (28)].

FVP of 5c (1.09 g) gave a yellow liquid which was subjected to preparative TLC (SiO₂/Et₂O) to give two major fractions identified as N-methylacetamide **7c** [¹H NMR: 6.32 (1H, br. s, NH), 2.79 and 2.77 (3H, 2 × s, NMe of *E*- and *Z*-rotamers), 1.98 (3H, s, COMe); ¹³C NMR: 171.3, 26.3, 22.8; *m/z* 73 (M⁺, 60%), 58 (40), 43 (100)] and acetonitrile **8c** [¹H NMR: 2.02 (s); ¹³C NMR 116.5, 1.8].

FVP of 5d (1.01 g) gave a yellow liquid which was subjected to preparative TLC (SiO₂/Et₂O) to give two major fractions identified as N-ethylacetamide **7d** [¹H NMR: 6.10 (1H, br. s, NH), 3.29 and 3.28 (2H, 2 × q, *J* = 7 Hz, NCH₂ of *E* and *Z* rotamers), 1.98 (3H, s), 1.14 (3H, t, *J* = 7 Hz); *m/z* 87 (M⁺, 51%), 72 (18), 43 (100)] and propionitrile **8d** [¹H NMR: 2.37 (2H, q, *J* = 7 Hz), 1.31 (3H, t, *J* = 7 Hz)].

FVP of 5f (1.10 g) gave a yellow liquid which was subjected to preparative TLC (SiO₂/Et₂O) to give two major fractions identified as N-butylacetamide **7f** [¹H NMR: 5.80 (1H, br. s, NH), 3.24 and 3.22 (2H, 2 × t, *J* = 7 Hz, NCH₂ of *E*- and *Z*-rotamers), 1.98 (3H, s), 1.52 (2H, m), 1.36 (2H, m), 0.93 (3H, *J* = 7 Hz); *m/z* 115 (M⁺, 10%), 100 (20), 86 (20), 72 (62), 43 (100)] and valeronitrile **8f** [¹H NMR: 2.35 (2H, t, *J* = 7 Hz), 1.65 (2H, m), 1.48 (2H, m), 0.96 (3H, t, *J* = 7 Hz)].

FVP of 6c (1.10 g) gave a yellow liquid which was subjected to preparative TLC (SiO₂/Et₂O) to give two major fractions identified as N-methylacetamide **7c** [¹H and ¹³C NMR and MS as for **5c**] and acetonitrile **8c** [¹H and ¹³C NMR as for **5c**].

REFERENCES

1. J. Correia, *J. Org. Chem.*, **38**, 3433 (1973).
2. H. Bartsch, W. Kropp, and M. Pailer, *Monatsh. Chem.*, **110**, 257 (1979).
3. C. Barkenbus and P. S. Landis, *J. Am. Chem. Soc.*, **70**, 684 (1948).
4. R. A. Aitken, P. K. G. Hodgson, A. O. Oyewale, and J. J. Morrison, *Chem. Commun.*, 1163 (1997).
5. M. Sido, *Ber. Dtsch. Pharm. Ges.*, **31**, 118 (1921).
6. J. F. Wolfe and T. G. Rogers, *J. Org. Chem.*, **35**, 3600 (1970).
7. H. Staudinger and E. Hauser, *Helv. Chim. Acta*, **4**, 887 (1921).
8. H.-W. Winter and C. Wentrup, *Angew. Chem., Int. Ed. Engl.*, **19**, 720 (1980).
9. J. August, K. Klemm, H. W. Kroto, and D. R. M. Walton, *J. Chem. Soc., Perkin Trans. 2*, 1841 (1989).
10. J.-L. Ripoll, H. Lebrun, and A. Thuillier, *Tetrah. Lett.*, 463 (1978).
11. B. De Corte, J.-M. Denis, and N. De Kimpe, *J. Org. Chem.*, **52**, 1147 (1987).
12. H. Quast, H. Leybach, and E.-U. Würthwein, *Chem. Ber.*, **125**, 1249 (1992).
13. I. Lengyel and J. C. Sheehan, *Angew. Chem., Int. Ed. Engl.*, **7**, 25 (1968).
14. J. M. Patterson, C.-Y. Shiue, and W. T. Smith, *J. Org. Chem.*, **38**, 2447 (1973).
15. J.-C. Guillemin and J.-M. Denis, *Tetrahedron*, **44**, 4431 (1988).
16. R. A. Aitken and A. W. Thomas, *Arkivoc*, **2**, in press (2001).