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Heterocyclic Synthesis with Azides. I The Reaction of Hydrazoic Acid with Ethoxymethylenemalonate

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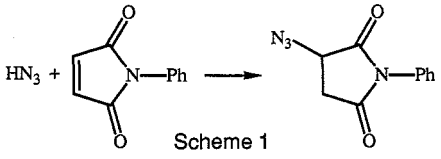
Abstract

Reaction of diethyl ethoxymethylenemalonate with sodium azide in trifluoroacetic acid at 20° gives ethyl 5-ethoxyisoxazole-4-carboxylate (67%), diethyl cyanomalonate (21%) and diethyl ethoxyaminomethylenemalonate (5%). The last compound and its tautomer are converted into ethyl 1-ethoxy-3-oxo-2,3-dihydro-1*H*-pyrazole-4-carboxylate. The product stuctures have been confirmed by synthesis or degradation.

Introduction

Although alkyl and aryl azides undergo cycloadditions with alkenes bearing electron-withdrawing groups, reactions which are relatively well understood,[1,2] the reaction of hydrazoic acid with such alkenes usually consists only of addition[3,4] (Scheme 1). However, cycloaddition of hydrazoic acid to a conjugated ester has been reported,[5] perhaps induced by the subsequent formation, in that case, of an aromatic triazole.



Scheme 1

Where acid-catalysed Michael additions are not possible, hydrazoic acid then generally does not react, unless the alkene is strained[6] or Lewis acid catalysts are used.[7] Electron-donating groups, such as found in enol ethers, allow rapid uncatalysed additions.[8] Since cycloadditions in all these cases were rarely observed,

[1] Huisgen, R., Szeimies, G., and Moebius, L., *Chem. Ber.*, 1967, **100**, 2494.
[2] Huisgen, R., *Angew. Chem., Int. Ed. Engl.*, 1963, **2**, 565, 633.
[3] Awad, W. I., Omran, S. M. A. R., and Nagiel, F., *Tetrahedron*, 1963, **19**, 1591.
[4] Boyer, J. H., *J. Am. Chem. Soc.*, 1951, **73**, 5248.
[5] Fisera, L., Povazanec, F., Zalupsky, P., Kovac, J., and Pavlovic, D., *Collect. Czech. Chem. Commun.*, 1983, **48**, 3144.
[6] Hassner, A., and Galle, J. E., *J. Am. Chem. Soc.*, 1972, **94**, 3930.
[7] Hassner, A., Fibiger, R., and Andisik, D., *J. Org. Chem.*, 1984, **49**, 4237.
[8] Washbourne, S. S., and Peterson, W. R., *J. Organomet. Chem.* 1970, **21**, 427.

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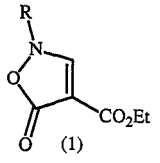
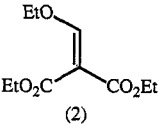
synthetic equivalents such as trimethylsilyl azide[9] or benzyl azide are generally used when this mode of reaction is desired. We have been studying the reactions of various *N*-substituted isoxazolones (1)[10] with hydrazoic acid and azide anion, and that study has led us to examine the simpler analogue, ethoxymethylenemalonate (2). In this communication we detail the nature of the products obtained from the reaction of hydrazoic acid with diethyl ethoxymethylenemalonate (2).



(1)

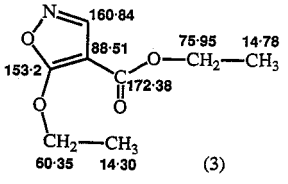


(2)

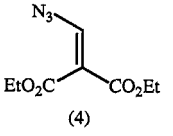
Discussion

Reaction of the ethoxymethylenemalonate with sodium azide in trifluoroacetic acid at 20° led to the detection of seven products by analytical h.p.l.c., and all of these were isolated and characterized by a combination of chromatographic techniques. The major product (67%), best obtainable by h.p.l.c. or radial chromatography, but also by direct distillation of the reaction mixture, was a low-melting colourless solid, whose structure was deduced to be ethyl 5-ethoxyisoxazole-4-carboxylate (3).

The infrared spectrum showed the presence of the ester (1717 cm^{-1}) and the aromatic ring (1615 cm^{-1}). The ^1H n.m.r. spectrum showed a sharp singlet for H3 at δ 8·43, and the presence of two non-equivalent ethoxy groups. The ^{13}C n.m.r. spectrum then allowed the structure to be deduced [cf. chemical shift data shown on the structural formula of (3)].



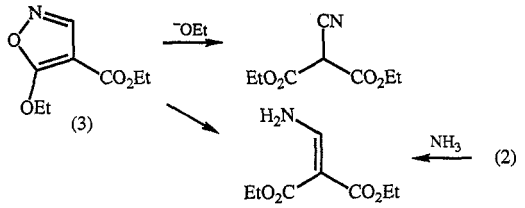
(3)



(4)

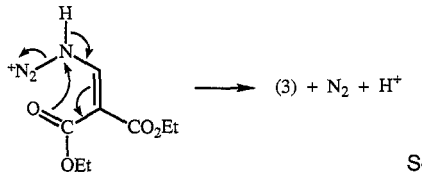
The proposed structure was confirmed by reaction with sodium ethoxide in ethanol, which brought about the characteristic isoxazole bond cleavage[11] to give diethyl cyanomalonate, identified by its spectral properties[12] and by synthesis.[13] Hydrogenation of (3) gave diethyl aminomethylenemalonate, identified by comparison with a sample prepared from diethyl ethoxymethylenemalonate (2) and ammonia (Scheme 2).

[9] Washbourne, S. S., Peterson, W. R., and Berman, D. A., *J. Org. Chem.*, 1972, **37**, 1738.
[10] Donati, C., Janowski, W. K., Prager, R. H., Taylor, M. R., and Vilkins, L. M., *Aust. J. Chem.*, 1989, **42**, 2161.
[11] Barnes, R. A., in 'Heterocyclic Compounds' (Ed. R. C. Elderfield) Vol. 5, p. 453 (John Wiley: New York 1957).
[12] Mignonac, G., Miguel, R., and Bonnemaison, C., *Bull. Soc. Chim. Fr.*, 1958, 1323.
[13] Haller, A., *C. R. Acad. Sci.*, 1898, **105**, 169.



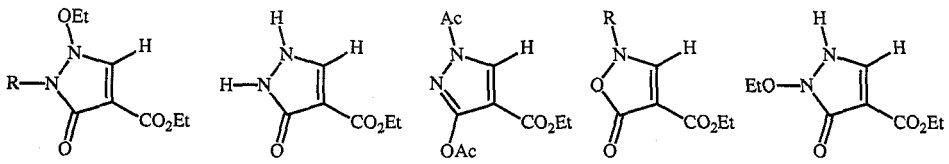
Scheme 2

Finally, the structure of (3) was confirmed by comparison of its properties with those reported by Klaus and Thieme,[14] who obtained (3) by heating the azido ester (4) in boiling toluene. Although, in that case, the isoxazole (3) probably arises from the nitrene generated from (4), in the reaction described by us it is most likely that (3) arises directly from the protonated azide (Scheme 3).



Scheme 3

The second product, best obtained by direct distillation of the reaction mixture, whereupon it was obtained as colourless needles (10%), m.p. 94–96°, was assigned the structure ethyl 2-ethoxy-5-oxo-3-pyrazoline-4-carboxylate (5). Compound (5) was obtained when a large excess of azide was used, and was replaced by compounds (12) and (13) under normal conditions.



(5) R = H
(6) R = Ac

(7)

(8)

(9) R = H
(10) R = Ac

(11)

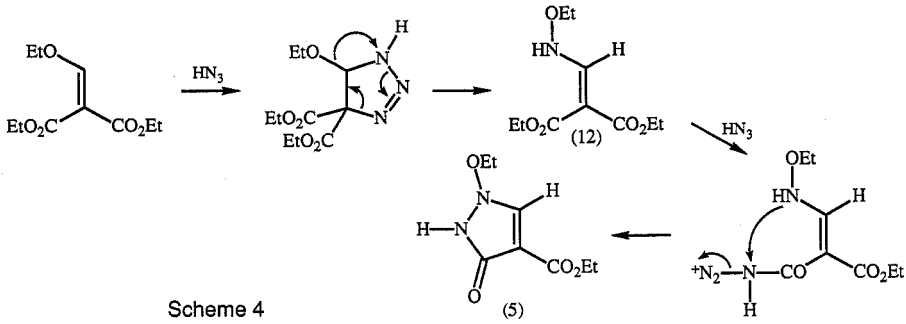
The neutral compound (5), $C_8H_{12}N_2O_4$, had NH (3144 cm^{-1}), ester (1715 cm^{-1}) and lactam (1705 cm^{-1}) groups typical of pyrazolin-5-ones.[15] The ^1H n.m.r. spectrum showed the presence of two ethoxy groups, and a single proton at 9·50 ppm. The ^1H n.m.r. spectrum of the *N*-acetyl derivative (6) retained the vinyl resonance at 7·25 ppm, whereas the 3-pyrazolin-5-one (7) had H3* resonating at δ 7·60, shifted to 8·63 on diacetylation to (8), and the isoxazol-5-one (9) had H3 resonate at 8·30 ppm, with H3 in the acetyl derivative (10) resonating at 9·00 ppm. We

* Systematic names based on pyrazole (rather then pyrazoline), e.g. ethyl 1-ethoxy-3-oxo-2,3-dihydro-1*H*-pyrazole-4-carboxylate (5) (see Experimental), require this proton to become H5.

[14] Klaus, F., and Thieme, H. K., *Chem. Ber.*, 1970, **103**, 1982.
[15] Elguero, J., Mazin, C., Katritzky, A. R., and Linda, P., *Adv. Heterocycl. Chem.*, 1976, 1, 313.

believe that this evidence allows a clear distinction to be drawn between the isomeric structures (5) and (11).

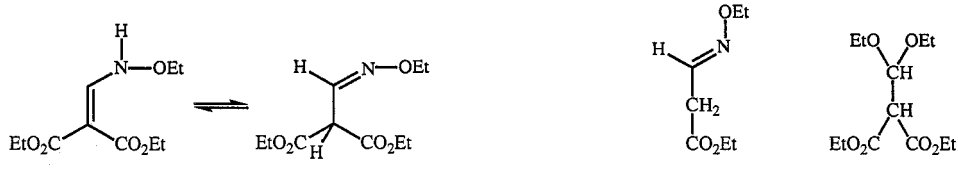
We suggest that (5) is formed by a pathway similar to that shown in Scheme 4, involving 2 equiv. of hydrazoic acid.



Scheme 4

The third product isolated by h.p.l.c. from the original hydrazoic acid reaction was diethyl cyanomalonate (21%). This compound appeared to be largely in the enolic form, as judged by its infrared spectrum (3416, 2195, 1676 cm^{-1}), and its reaction with ferric chloride.[12] Its structure was confirmed by direct comparison with an authentic sample.[13]

The remaining products (5%), isolated by h.p.l.c. or t.l.c., were tautomers or stereoisomers of diethyl ethoxyaminomethylenemalonate (12). The tautomer (12) was characterized by its ^1H n.m.r. spectrum, which showed the NH (13·5 ppm) to be coupled to the single proton at 8·35 ppm.



(12) (13) (14) (15)

The tautomer (13), which could be separated from (12) by h.p.l.c., but rapidly reestablished the equilibrium, was characterized by the sets of doublets for the (*E*) and (*Z*) isomers at δ 3·95 and 7·50 (J 8 Hz), and 4·85 and 7·00 (J 5 Hz). To confirm the identity of these compounds, they were synthesized by reaction of *O*-ethylhydroxylamine with ethoxymethylenemalonate. When the hydrochloride of the former was refluxed in ethanol with (2), the major tautomer isolated was (13), with both (*E*) and (*Z*) isomers in the ratio of 1:1, and only traces of the tautomer (12). Longer reaction times resulted in de-ethoxycarbonylation, presumably induced by chloride attack on the ethyl ester in (13), to give the oxime ether (14). Under basic conditions, the ethoxymethylenemalonate and *O*-ethylhydroxylamine gave essentially only the tautomer (13), accompanied by the base-calatysed ethanol addition product, diethyl diethoxymethylmalonate (15).

In conclusion, it is apparent that a conjujated enol ether represents a reactive target for hydrazoic acid, and the products can be interpreted as arising from

rearrangement of a protonated azide, or by rearrangement of an initial cycloaddition product.

Experimental

The general experimental details have already been published.[16]

Reaction of Diethyl Ethoxymethylenemalonate with Sodium Azide in Trifluoroacetic Acid

Diethyl ethoxymethylenemalonate (5·0 g, 20 mmol) was stirred with sodium azide (8·0 g, 123 mmol) in trifluoroacetic acid (50 ml) for 12 h. The mixture was evaporated to dryness, aqueous sodium bicarbonate added, and the mixture extracted with ethyl acetate to yield a red oil (5·0 g). A portion (600 mg) was distilled, giving a liquid fraction, b.p. 140°/0·1 mm, and a colourless solid, b.p. 160°/0·1 mm. The liquid was purified by radial chromatography on silica. Light petroleum yielded a white solid (400 mg, 67%), purified by sublimation to give ethyl 5-ethoxyisoxazole-4-carboxylate (3), m.p. 38–40° (lit.[14] 41°) (Found: C, 51·8; H, 6·1; N, 7·4. Calc. for $C_8H_{11}NO_4$: C, 51·9; H, 6·0; N, 7·6%). ν_{max} 1717, 1615, 1527 cm^{-1}. ^1H n.m.r. δ 1·35, t, J 7 Hz, 3H; 1·47, t, J 7 Hz, 3H; 4·23, q, J 7 Hz, 2H; 4·59, q, J 7 Hz, 2H; 8·43, s, 1H. ^{13}C n.m.r. δ 14·30, CH_3; 14·78, CH_3; 60·35, CH_2; 75·95, CH_2; 88·51, C4; 153·20, C5; 160·84, C3; 172·38, CO. λ_{max} 226 nm (ϵ 24987).

The colourless solid was resublimed to give *ethyl 1-ethoxy-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate* (5) as colourless needles (60 mg, 10%) (Found: C, 48·2; H, 5·8; N, 13·7%; $M^{+\bullet}$, 200·0797. $C_8H_{12}N_2O_4$ requires C, 48·0; H, 6·0; N, 14·0%; $M^{+\bullet}$, 200·0797). ν_{max} 3144, 1715, 1705, 1598 cm^{-1}. ^1H n.m.r. δ 1·35, t, J 8 Hz, 6H; 4·21, q, J 8 Hz, 4H; 7·25, s, 1H; 9·50, br, 1H, exch. Mass spectrum m/z 200 (M), 172, 156, 128, 110. ^{13}C n.m.r. δ 13·33, CH_3; 14·25, CH_3; 61·22, CH_2; 74·22, CH_2; 109·27, C4; 117·29, C5; 149·41, CO; 159·06, CO.

The remaining reaction product (4·00 g) was separated on silica by h.p.l.c., by elution with light petroleum/ethyl acetate, 4:1. The first product eluted was ethyl 5-ethoxyisoxazole-4-carboxylate (2·50 g, 64%). The second was a colourless oil (500 mg, 21%) identified as diethyl cyanomalonate, which gave a blood red ferric chloride test,[12] yielding black needles in ether.[12] ν_{max} 3416, 2195, 1676, 1583 cm^{-1}. ^1H n.m.r. δ 1·25, t, J 7 Hz, 6H; 4·10, q, J 7 Hz, 4H; 3·25, br, 1H, exch. An authentic sample was prepared by the method of Haller,[13] and was identical in every respect with this product.

The third fraction (300 mg, 5%) was isolated as a colourless oil, and was shown by ^1H n.m.r. spectroscopy to be a mixture of *diethyl* N-*ethoxyaminomethylenemalonate* (12) and the (*E*) and (*Z*) isomers of *diethyl* N-*ethoxyiminomethylmalonate* (13) in the ratio of 2:1 (*E* to *Z* 1:1). ^1H n.m.r. of (12): δ 1·25, m, 9H; 4·17, m, 6H; 8·35, br d, J 10 Hz, 1H, exch. ν_{max} 3218, 1649, 1600 cm^{-1}. ^1H n.m.r. of (13): δ 1·25, m, 9H; 4·17, m, 6H; 3·95, d, J 8 Hz, and 4·85, d, J 5 Hz, 1H; 7·00, d, J 5 Hz, 1H; 7·50, d, J 8 Hz, 1H. ν_{max} 1735 cm^{-1}. Kugelrohr distillation (80°/0·01 mm) gave a pure sample of (12) (Found: C, 51·8; H, 7·8. $C_{10}H_{17}NO_5$ requires C, 51·9; H, 7·4%). Mass spectrum m/z 232 (M+1), 217, 203, 189, 186, 158.

The fourth fraction contained small quantities (total <10%) of a number of compounds, including ethyl 1-ethoxy-3-oxo-2,3-dihydro-1*H*-pyrazole-4-carboxylate, but no pure material could be obtained.

Reactions of Ethyl 5-Ethoxyisoxazole-4-carboxylate (3)

(i) *With sodium ethoxide.* Isoxazole (3) (100 mg) was refluxed with sodium ethoxide [from sodium (50 mg) and ethanol (10 ml)] for 30 min. The solvent was removed, dilute HCl added, and the mixture extracted with ethyl acetate to yield diethyl cyanomalonate (100 mg) as a colourless oil. This was identical in every respect with an authentic sample, made by the method of Haller.[13]

(ii) *Hydrogenation.* Isoxazole (3) (200 mg) was hydrogenated at 4 atm and 20° in the presence of 5% palladium on carbon in ethanol (100 ml). After 10 h, the catalyst and solvent were removed to yield a colourless solid, m.p. 59° (190 mg, 94%), identified as diethyl

[16] Prager, R. H., Tsopelas, C., and Heisler, T., *Aust. J. Chem.*, 1991, **44**, 277.

aminomethylenemalonate (lit.[17] m.p. 65°) (Found: $M^{+\bullet}$, 187·0905. Calc. for $C_8H_{13}NO_4$: $M^{+\bullet}$, 187·0844). ^{1}H n.m.r. δ 1·30, t, J 7 Hz; 1·40, t, J 7 Hz, 3H; 4·12, q, J 7 Hz, 2H; 4·25, q, J 7 Hz, 2H; 6·50, br, 2H, exch.; 8·30, s after D_2O, 1H. ν_{max} 3386, 3302, 3241, 1724, 1667, 1625 cm^{-1}.

The material from (ii) was identical with a sample obtained by refluxing ethyl ethoxymethylenemalonate with ethanol saturated with ammonia for 1 h.

Ethyl 2-Acetyl-1-ethoxy-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate (6)

Ethyl 1-ethoxy-3-oxo-2,3-dihydro-1*H*-pyrazole-4-carboxylate (5) (160 mg) was stirred with acetic anhydride (2 ml) overnight. The solvent was removed, and the *solid* recrystallized from ethanol as colourless needles (160 mg, 83%), m.p. 50–52° (Found: C, 49·5; H,, 5·8%; $M^{+\bullet}$, 242·0903. $C_{10}H_{14}N_2O_5$ requires C, 49·6; H, 5·8%; $M^{+\bullet}$, 242·0903). ν_{max} 1741, 1604 cm^{-1}. ^{1}H n.m.r. δ 1·34, t, J 8 Hz, 6H; 2·70, s, 3H; 4·21, q, J 8 Hz, 4H; 7·25, s, 1H.

Ethyl 3-Acetoxy-1-acetyl-1H-pyrazole-4-carboxylate (8)

Ethyl 3-oxo-2,3-dihydro-1*H*-pyrazole-4-carboxylate (7) (200 mg) was acetylated as above. The *title compound* (270 mg, 90%) was recrystallized from ethanol as colourless crystals, m.p. 78–80° (Found: C, 49·9; H, 5·0; N, 11·4. $C_{10}H_{12}N_2O_5$ requires C, 50·0; H, 5·0; N, 11·7%). ν_{max} 1781, 1750, 1574, 1521 cm^{-1}. ^{1}H n.m.r. δ 1·35, t, J 7 Hz, 3H; 2·37, s, 3H; 2·66, s, 3H; 4·22, q, J 7 Hz, 2H; 8·63, s, 1H.

Reaction of O-Ethylhydroxylamine with Diethyl Ethoxymethylenemalonate

(i) A mixture of diethyl ethoxymethylenemalonate (1·49, 6·0 mmol) and *O*-ethylhydroxylamine hydrochloride[18] (0·6 g, 6·0 mmol) was refluxed in ethanol (25 ml) for 12 h. The solvent was removed, sodium hydroxide added, and the mixture extracted with ethyl acetate to yield a pale yellow oil (1·5 g), shown by n.m.r. spectroscopy to contain a 1 : 1 mixture of the (*E*) and (*Z*) isomers of diethyl ethoxyiminomethylmalonate (13) (82%) and diethyl ethoxyaminomethylenemalonate (12) (18%), identical with the samples identified above.

(ii) A similar reaction to the above, in dimethyl sulfoxide, gave only diethyl ethoxyiminomethylmalonate (13) (90%).

(iii) When the reaction time in ethanol was prolonged to 18 h, distillation of the product gave 68% of a colourless oil, b.p. 55–60°/0·1 mm, identified as *ethyl 3-ethoxyiminopropionate* (14) (Found: C, 53·0; H, 7·9; N, 8·6. $C_7H_{13}NO_3$ requires C, 52·8; H, 8·2; N, 8·6%). ν_{max} 1741, 1633 cm^{-1}. ^{1}H n.m.r. δ 1·30, t, J 7 Hz, 3H; 1·35, t, J 7 Hz, 3H; 3·25, d, J 5 Hz, and 3·4, d, J 6 Hz, 2H; 4·21, m, 4H; 6.98, t, J 5 Hz, 1H (*Z* isomer); 7·48, t, J 6 Hz, 1H (*E* isomer). The pot residue consisted of diethyl ethoxyiminomethylmalonate (32%).

(iv) The use of sodium acetate in the reaction, otherwise identical with (i), gave a mixture of (*E*) and (*Z*) isomers (1:1) of diethyl ethoxyiminomethylmalonate (66%) and diethyl diethoxymethylmalonate (15) (33%), identified by comparison with an authentic sample.

Acknowledgments

A.D. is grateful to the Government of Ghana, and the Australian International Assistance Bureau for a scholarship. The project was supported by the Australian Research Council.

[17] Claisen, L., *Justus Liebigs Ann. Chem.*, 1897, **297**, 77.

[18] Bruno, J. R., Tesor, E., Nicolaus, J. R., Mariani, L., and Pagani, G., *Ann. Chim. (Rome)*, 1963, **53**, 281 (*Chem. Abstr.*, 1963, **59**, 3814).