The Scope and Mechanism of a Novel Synthesis of 3,4-Fused Isoxazoles

Kevin J. Duffy and George Tennant*

Department of Chemistry, University of Edinburgh, West Mains Road, Edinburgh, UK EH9 3JJ

Thermal cyclisation of 2-nitrophenyl- and 3-nitrohetaryl-ethanoate derivatives in xylene is facilitated indirectly by 5 Å molecular sieves affording an efficient general method for the construction of synthetically useful 3,4-fused isoxazoles; evidence for the mechanism of these novel heterocyclisation reactions is presented.

Monocyclic isoxazoles are widely exploited[1] through reductive ring scission as a valuable source of synthetically useful β-enamino carbonyl compounds. In contrast, the paucity[2] of synthetic methods for usefully functionalised isoxazoles fused to a second ring through the 3,4-bond (2,1-benzisoxazoles[2] apart), limits the value of such structures as a corresponding source of condensed *ortho*-amino carbonyl compounds. As part of a programme of research concerned with the design of sequence specific DNA major groove-binding molecules[3] we required flexible access to appropriately substituted 3,4-fused isoxazoles for further elaboration to highly functionalised, condensed polynuclear polyazaheterocycles. Here we report an efficient general method for the synthesis of 3,4-fused isoxazoles based on the solution phase thermolysis of readily accessible 2-nitrophenyl- and 3-nitrohetaryl-ethanoates and provide evidence for the mechanism of these novel heterocyclisation reactions.

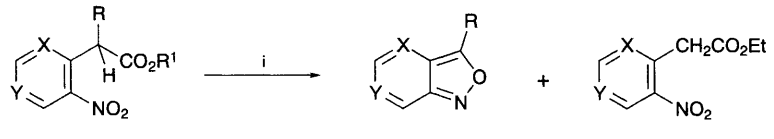
The direct interaction of aromatic nitro groups with electrophilic centres in *ortho* side-chains is a fruitful if somewhat neglected approach to the synthesis of a wide variety of heterocycles, including 2,1-benzoisoxazoles.[4] Of particular significance in the context of 3,4-fused isoxazole synthesis in general is the hitherto unauthenticated report by Grob and Weissbach[5] that distillation of diethyl 2-(2-nitrophenyl)propanedioate occurs with concomitant cyclisation to ethyl 2,1-benzisoxazole-3-carboxylate, though in unspecified yield. The potential of this unusual heterocyclisation reaction as a general method for the synthesis of 3,4-fused isoxazoles from easily accessible starting materials prompted the present investigation of its efficiency, scope and mechanism (Schemes 1 and 2).

The 2-nitrophenyl- and 3-nitrohetaryl-ethanoate derivatives **1** and **4** studied were readily accessible in uniformly high yield (70–90%) by the S_NAr reactions of 2-fluoronitrobenzene or the corresponding *ortho*-chloronitro-pyridine or -pyrimidine derivatives with the appropriate stabilised carbanions under standard conditions. Contrary to the findings of Grob and Weissbach,[5] diethyl 2-(2-nitrophenyl)propanedioate **1a** was found in the present studies to distil substantially unchanged with no evidence for the formation of the 2,1-benzisoxazole derivative **2a**. The diester **1a** was also unaffected by prolonged (48 h) heating under reflux in anhydrous xylene. The corresponding pyridine derivative **1c** was equally inert (recovery 90–100%) to heating in the absence of solvent under reduced pressure (110–120 °C/0.3 mm Hg) or to extended heating under reflux in anhydrous xylene (120 h).

The transformation (**1a** → **2a**) described by Grob and Weissbach[5] is a redox process involving the formal loss of ethanol and carbon dioxide. On the assumption that successful cyclisation might be dependent on the removal of the ethanol produced, the pyridinylpropanedioate **1c** was heated under reflux in xylene for 24 h with continuous fractionl distillation to remove any ethanol present. Under these conditions the previously undescribed ethyl isoxazolopyridine-carboxylate **2c** was formed in high yield together with a small amount of the nitropyridinylethanoate **3b** (Table 1). The corresponding methyl ester **2b** was formed analogously in high yield (Table 1) from the dimethyl ester **1b**. Heating the diester **1c** in xylene with entrainment of the ethanol produced in a stream of nitrogen also gave the isoxazolopyridine derivative **2c** in high yield (Table 1).

In an attempt to improve the convenience of the cyclisation process while maintaining its efficiency, the thermal cyclisation of the pyridinylpropanedioate **1c** in xylene was conducted in the presence of 5 Å molecular sieves chosen on the basis of a cavity size appropriate for the occlusion of ethanol. However even after 72 h under these conditions, the isoxazolopyridine derivative **2c** was formed only in moderate yield (52%). In marked contrast, heating the diester **2c** under reflux in xylene for 24 h with passage of the condensed solvent over 5 Å molecular sieves in a soxhlet extractor afforded the isoxazolopyridine derivative **2c** in excellent yield (Table 1). The facilitating effect† of molecular sieves external to the reaction mixture is surprising but can be attributed to the displacement of an otherwise unfavourable equilibrium in favour of the cyclic product presumably by removal of ethanol produced in the early stages of cyclisation as adduced on mechanistic grounds. Passage of the condensed solvent over 5 Å molecular sieves in a soxhlet extractor also promoted the previously unsuccessful cyclisation (**1a** → **2a**) in high yield (Table 1) albeit with a longer reaction time than that of the pyridine derivative **1c**.

The precise *modus operandi* of the 5 Å molecular sieves in promoting the efficient cyclisation of the diesters **1a** and **1c** to the 3,4-fused isoxazoles **2a** and **2c** is not entirely clear at present. Physical occlusion of the ethanol produced on thermolysis is in accord with the cavity size of 5 Å molecular sieves. Promotion of cyclisation by this means is consistent with the efficient cyclisation of the dimethyl ester **1b** under reflux in

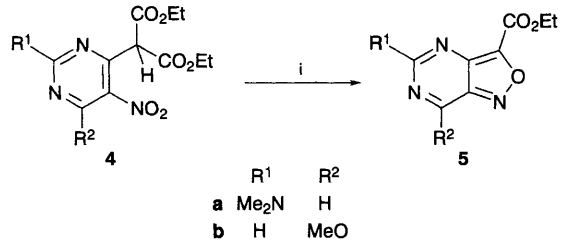


1	X	Y	R	R^1
a	CH	CH	CO_2Et	Et
b	N	CH	CO_2Me	Me
c	N	CH	CO_2Et	Et
d	N	CH	CO_2CH_2Ph	CH_2Ph
e	N	CH	COMe	Et
f	N	CH	COPh	Et
g	N	CH	CN	Et
h	CH	N	CO_2Et	Et

2	X	Y	R
a	CH	CH	CO_2Et
b	N	CH	CO_2Me
c	N	CH	CO_2Et
d	N	CH	CO_2CH_2Ph
e	N	CH	COMe
f	N	CH	COPh
g	N	CH	CN
h	CH	N	CO_2Et

3	X	Y
a	CH	CH
b	N	CH
c	CH	N

Scheme 1 *Reagents and conditions*: i, see Table 1



Scheme 2 *Reagents and conditions*: i, see Table 1.

Table 1

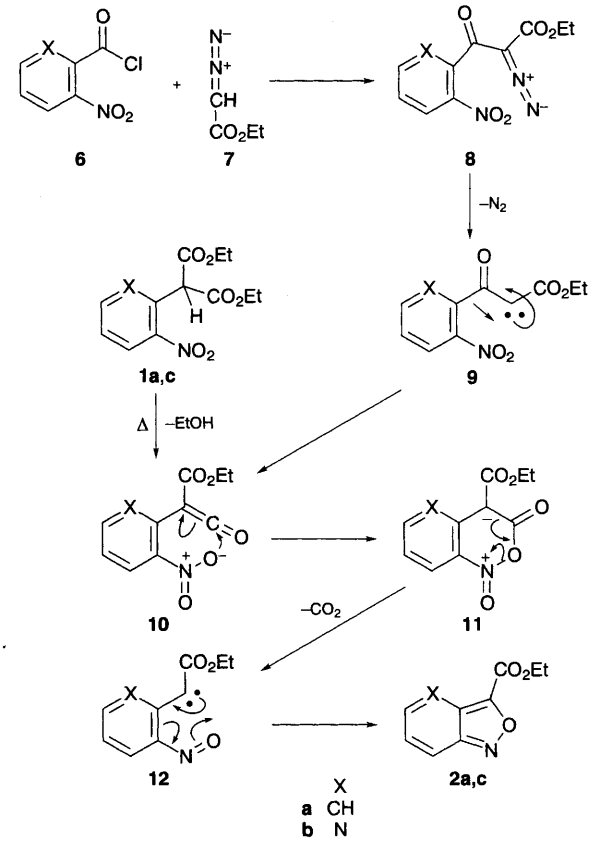
Substrate(s)/ reaction conditions[a]	Product[b]	Yield (%)[c]	Mp/°C
1a[d]	**2a**	63(75)	62[e]
1b[f]	**2b**	100	139
1b	**2b**	78	—
1c[f]	**2c**[g]	95	102
1c[h]	**2c**	87	—
1c	**2c**	95	—
1e[i]	**2e**	43	100
1f	**2f**	31	126
1g[i]	**2g**	83	86
1h[j]	**2h**[k]	69	80
4a[l]	**5a**	79	163
4b	**5b**	67	108

[a] Reflux in anhydrous xylene for 24 h with continuous passage of the condensed solvent over 5 Å molecular sieves (3–6 g $mmol^{-1}$ of substrate) in a soxhlet extractor for 21 h, unless otherwise specified. [b] Satisfactory elemental combustion analyses and mass, IR and ^1H NMR spectral data were obtained for all new compounds. [c] Yields are unoptimised; figures in parenthesis refer to yields based on unrecovered starting material. [d] Reaction time 100 h. [e] Lit.,[5] 67 °C. [f] Reflux in anhydrous xylene for 24 h with continuous removal of the methanol or ethanol formed, by fractional distillation. [g] **3b** (yield 3%), orange oil, bp 120–125 °C/1.6 mmHg also isolated. [h] Reflux in anhydrous xylene with continuous removal of the ethanol formed by entrainment with nitrogen. [i] Reaction time 48 h. [j] Reaction time 96 h. [k] **3c** (yield 7%), yellow oil, bp 120–125 °C/0.2 mmHg also isolated. [l] Reaction time 18 h.

xylene with passage of the condensed solvent over 5 Å molecular sieves (Table 1) and the contrasting total failure of the dibenzyl ester **1d** (recovery 94%) to cyclise to the isoxazolopyridine derivative **2d** under similar conditions. In the latter case the 5 Å molecular sieves cannot occlude the bulkier benzyl alcohol produced by thermolysis.

Successful cyclisation to the corresponding isoxazolopyridine derivatives in refluxing xylene externally promoted by 5 Å molecular sieves also extended to the keto-esters **1e** and **1f** and the cyano-ester **1g** as well as the pyridin-4-yl diester **1h** and the pyrimidin-4-yl diesters **4a** and **4b** (Table 1). In the cases of the keto-esters **1e** and **1f** the yields of cyclised products were somewhat lower than in the other cyclisation reactions. Also isolated in the cyclisation of the diester **1h** was a low yield (Table 1) of the uncyclised propanoate **3c**. Grob and Weissbach[5] reported the co-formation of ethyl 2-nitrophenylethanoate **3a** in their cyclisation of the diester **1a** to the 2,1-benzisoxazole derivative **2a**.

The thermal transformations of the ethyl nitrophenyl- and nitrohetaryl-ethanaotes **1** and **4** into the corresponding 3,4-fused isoxazoles **2** and **5** can be rationalised by a mechanism (Scheme 3) initiated by extrusion of alcohol to give a ketene intermediate **10**, a process known[6] to occur with other diethyl propanedioate derivatives. Nucleophilic interaction of the *ortho*-nitro group with the ketene side-chain in **10**, by analogy with other known[7] *ortho*-nitro group-heterocumulene interactions would then afford a cyclic betaine intermediate **11** convertible by loss of carbon dioxide and electrocyclisation of



Scheme 3

the resulting *ortho*-nitroso carbene intermediate **12** into the final product **2**. The first stage (**1** → **10**) of this proposed mechanism has been substantiated in the present studies by the independent generation and thermal cyclisation of the ketene derivatives **10a** and **10b**. Thus, condensation of the acid chlorides **6a** and **6b** with ethyl diazoacetate **7** in the absence of solvent at 50 °C gave good yields (77 and 57% respectively) of the diazo-keto-esters **8a** and **8b**. Thermolysis of these compounds by heating under reflux in anhydrous toluene gave the fused isoxazoles **2a** and **2c** in moderate yield (31 and 23% respectively) *via* the presumed intermediacy of the ketene derivatives **10a** and **10b** derived by Wolff rearrangement. In the thermolysis of the diazo-keto-ester **8a** the cyclic product **2a** was accompanied by the uncyclised mono ester **3a** (Yield 13%). The mode of formation of the latter is not clear at present though it could arise by decarbonylation of the ketene **10a** followed by hydrogen abstraction by the carbene species produced. In any case the formation of **3a** in the thermolysis of the diazo compound **8a** and of **3b** and **3c** in the thermolyses of the diesters **1c** and **1h** implies a common source and hence probably the corresponding ketene intermediates **10**.

We thank the University of Edinburgh for a research studentship.

Received, 31st August 1995; Com. 5/05764G

Footnote

† The specific removal of a volatile reaction component of a solution phase thermal process by external passage of the condensed reaction solvent through molecular sieves of appropriate cavity size appears to be a useful though, removal of water apart, an apparently rarely exploited procedure for

displacing otherwise unfavourable reaction equilibria in the direction of product.

References

1 B. J. Wakefield and D. J. Wright, *Adv. Heterocycl. Chem.*, 1979, 25, 186; P. Grunanger and P. Vita-Finzi, in *'Isoxazoles'*, ed. A. Weissberger and E. C. Taylor, Wiley, New York, 1991, vol. 49, pt. 1, ch. 1, pp. 273–281.

2 K. H. Wunsch and A. J. Boulton, *Adv. Heterocycl. Chem.*, 1967, **8**, 303; R. K. Smalley, *Adv. Heterocycl. Chem.*, 1981, **29**, 34; S. A. Lang and Y. I. Lin, in *'Comprehensive Heterocyclic Chemistry'*, ed. K. T. Potts, Pergamon, Oxford, 1984, vol. 6, ch. 4.16, pp. 120–127.

3 K. J. Duffy and G. Tennant, unpublished results.

4 J. D. Loudon and G. Tennant, *Quart. Rev. Chem. Soc.*, 1964, **18**, 389: P. N. Preston and G. Tennant, *Chem. Rev.*, 1972, **72**, 627.

5 C. A. Grob and O. Weissbach, *Helv. Chim. Acta*, 1961, **44**, 1748.

6 E. Ziegler and H. Sterk, *Monatsh. Chem.*, 1967, **98**, 1106.

7 J. M. Prokipcak and P. A. Forte, *Can. J. Chem.*, 1970, **48**, 3059; P. G. Houghton, D. F. Pipe and C. W. Rees, *J. Chem. Soc., Perkin Trans 1*, 1985, 1471.

8 A. Reissert and J. Sherk, *Chem. Ber.*, 1898, **31**, 387.