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The acid-mediated intramolecular 1,3-dipolar cycloaddition of derived 2-nitro-1,1-ethenediamines for the synthesis of novel fused bicyclic isoxazoles

Lee W. Page *, Matthew Bailey, Paul J. Beswick, Simon Frydrych, Robert J. Gleave

GlaxoSmithKline, New Frontiers Science Park, Third Avenue, Harlow, Essex CM19 5AW, UK

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ABSTRACT

The discovery of a novel synthesis of new fused bicyclic isoxazoles, for example, *N*-methyl-3-phenyl-5,6-dihydro-4*H*-isoxazolo[3,4-*c*]azepin-8-amine (**2a**), *N*-methyl-3-phenyl-4,5-dihydroisoxazolo[3,4-*c*]pyridin-7-amine (**2b**) and *N*-methyl-3-phenyl-4*H*-pyrrolo[3,4-*c*]isoxazol-6-amine (**2d**) in high yield is reported. We speculate that the reaction proceeds via acid-mediated intramolecular 1,3-dipolar cycloaddition from 2-nitro-1,1-ethenediamines **1a**,**b**,**d**.

The isoxazole ring is a commonly occurring structural fragment in biologically active molecules, for example, natural products such as muscimol and ibotenic acid[1] and marketed drugs (e.g., Valdecoxib, Bextra®).[2] Thus isoxazoles have been widely used and studied in modern drug discovery.[3]

Isoxazoles can be prepared in many ways, but the most widely reported and researched synthesis of isoxazoles is via a [3+2] cycloaddition of a nitrile oxide and an alkyne. Conventional generation of a nitrile oxide requires dehydration of a nitroalkane or similar starting material.[4–8] Other methods for generating nitrile oxides are by reaction of aldoximes with oxidising agents[9] or halogenating species[10] (in the latter case the reaction proceeds via hydroximoyl chlorides, followed by elimination of HCl with base).

Herein, we report the discovery and optimisation of a novel synthesis of previously unreported fused bicyclic isoxazoles **2a,b,d** (Fig. 1). We believe that the reaction proceeds via acid-mediated intramolecular 1,3-dipolar cycloaddition from 2-nitro-1,1-ethenediamines **1a**,**b**,**d**.

Treatment of 2-nitro-1,1-ethenediamine derivative **1a** with TFA at 70 °C affords the bicyclic isoxazole heterocycle **2a** in good yield (Scheme 1). This procedure exploits the ability of the 2-nitro-1,1-ethenediamine functionality to rearrange under acidic conditions. Recently, Coustard et al.[11] reported that similar intermediates could generate nitrile oxides in situ which subsequently cyclise intramolecularly onto a phenyl ring.[12] With our intermediates no cycloaddition onto the phenyl ring was observed. It is pertinent to note that this is, to the best of our knowledge, the first example

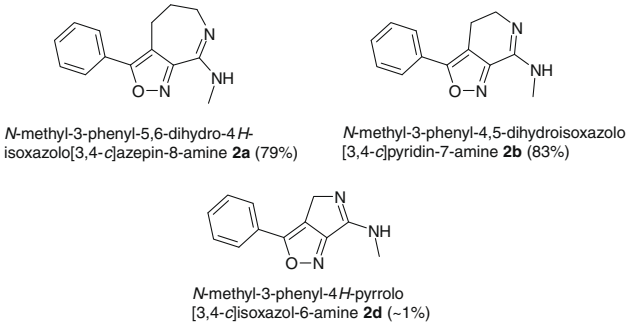
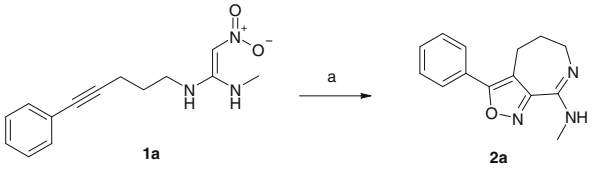


Figure 1. Novel bicyclic isoxazoles **2a**,**b**,**d** with isolated yields.



Scheme 1. Reagents and conditions: (a) TFA (10 equiv), MeCN, 70 °C, 24 h, followed by rt 48 h.

* Corresponding author. Tel.: +44 1279 643179; fax: +44 1279 622005.
E-mail addresses: Lee.W.Page@GSK.com, Lee.W.Page@live.com (L.W. Page).

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of the formation of an isoxazole via acid-mediated intramolecular 1,3-dipolar cycloaddition from 2-nitro-1,1-ethenediamines.

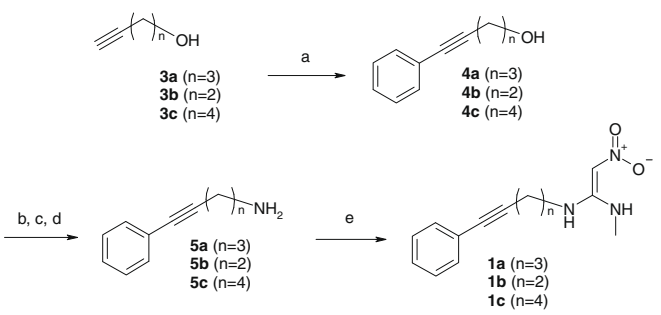
The procedure is versatile as the 2-nitro-1,1-ethenediamine derivatives can be readily prepared from a wide variety of amines using commercial reagents under mild conditions. Several synthetic approaches to intermediates **1a–d** were utilised. The route shown in Scheme 2 afforded alcohols **4a–c** via Sonogashira coupling with commercial acetylene alcohol derivatives **3a–c**.[13] Amines **5a–c** were prepared utilising Staudinger chemistry,[14] and subsequent treatment with *N*-methyl-1-(methylthio)-2-nitroethen-1-amine gave 2-nitro-1,1-ethenediamines **1a–c** in high yield.

2-Nitro-1,1-ethenediamine **1d** was prepared according to Scheme 3. Commercial 2-propyn-1-amine (**6**) was first treated with *N*-methyl-1-(methylthio)-2-nitroethen-1-amine to give the acetylene-nitro-etheneamine derivative **7**, and subsequent Sonogashira coupling afforded **1d**.

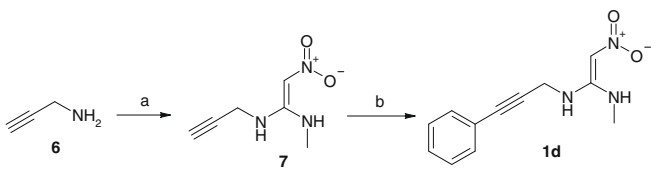
To determine optimal conditions rapidly several trial reactions against each variable were piloted. Each reaction was monitored crudely by UV absorbance percentage peak area, which was confirmed by observation of the product molecular ion using LC-MS.[15]

The studies show that the use of the microwave irradiation greatly reduces the reaction time whilst maintaining comparable yields to those of conventional thermal conditions. For example, cyclisation typically occurring in 2–3 h is comparable to 5 min with microwave irradiation (Table 1).

The data in Table 1 show that polar aprotic solvents are optimal solvents. Polar aprotic solvents are very efficient at absorbing microwave irradiation and are also good at solvating cations. This can lead to increased reactivity and improved reaction rates. Acetonitrile was the highest yielding solvent. Less polar solvents such as CH_2Cl_2 and THF performed poorly and some decomposition of the starting material was observed. Polar protic solvents (EtOH, water) were either very poor yielding or gave no product at all. It is likely that the hydrogen bonding abilities of the polar protic solvents could lead to solvent cage-like effects which stabilise intermediates and prevent product formation; reversibility on work-up could also explain the presence of starting materials in these cases.



Scheme 2. Reagents and conditions: (a) iodobenzene, $(Ph_3P)_2PdCl_2$, CuI, Et_3N, MeCN, 40 °C, 80–87%; (b) MsCl, Et_3N, CH_2Cl_2, rt, 80–91%; (c) NaN_3, DMF, 60 °C, 93–99%; (d) Ph_3P, THF, H_2O, 60 °C, 70–78%; (e) *N*-methyl-1-(methylthio)-2-nitroethen-1-amine, EtOH, H_2O, rt, 76–82%.



Scheme 3. Reagents and conditions: (a) *N*-methyl-1-(methylthio)-2-nitroethen-1-amine, EtOH, H_2O, rt, 80%; (b) iodobenzene, $(Ph_3P)_2PdCl_2$, CuI, Et_3N, MeCN, 40 °C, 82%.

Table 1
An investigation on multiple variables to optimise the synthesis of bicyclic isoxazoles **2a**,**b**,**d**

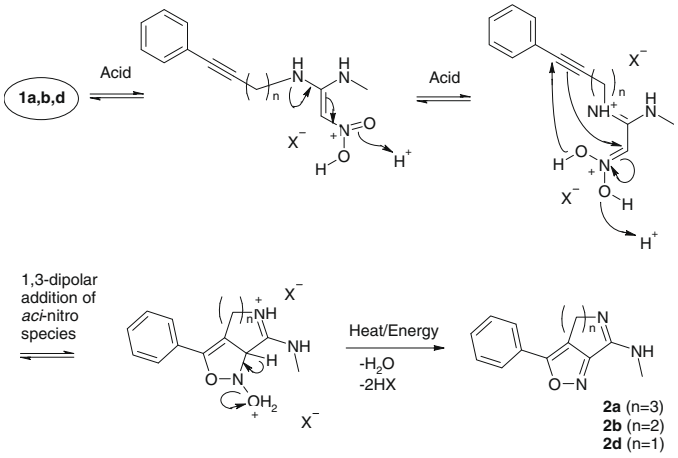
Substrate	Heat	Time (min)	*T* (°C)	Solvent	Product[a] (UV %)
1a	Δ	30	83	MeCN	**2a** (31)
1a	Δ	60	83	MeCN	**2a** (52)
1a	Δ	120	83	MeCN	**2a** (79)
1a	Δ	180	83	MeCN	**2a** (86)
1a	MW	5	140	MeCN	**2a** (78)
1a	MW	5	140	DMF	**2a** (57)
1a	MW	5	140	DMSO	**2a** (57)
1a	MW	5	140	THF	**2a** (21)
1a	MW	5	140	H_2O	**2a** (10)
1a	MW	5	140	EtOH	No product
1a	MW	5	140	CH_2Cl_2	**2a** (22)
1a	MW	0.5	140	MeCN	**2a** (69)
1a	MW	2	140	MeCN	**2a** (72)
1a	MW	10	140	MeCN	**2a** (76)
1a	MW	20	140	MeCN	**2a** (77)
1a	MW	5	100	MeCN	**2a** (65)
1a	MW	5	120	MeCN	**2a** (63)
1a	MW	5	160	MeCN	**2a** (77)
1b	MW	5	140	MeCN	**2b** (90)
1b	MW	10	120	MeCN	**2b** (86)
1b	MW	15	120	MeCN	**2b** (75)
1b	MW	10	100	MeCN	**2b** (32)
1d	MW	5	140	MeCN	**2d** (51)
1d	MW	5	120	MeCN	**2d** (27)
1d	MW	10	120	MeCN	**2d** (51)

Each reaction was conducted with 2 equiv of concd H_2SO_4 present.
[a] Results quoted as percentage area from the LC-MS UV trace.

Precise mechanistic details remain unclear. One suggested mechanism by Coustard et al.[11] uses a strong acid to generate a nitrile oxide in situ which would subsequently undergo 1,3-dipolar cycloaddition onto the alkyne. It is equally plausible that the 1,3-dipolar cycloaddition occurs via a stepwise process. Scheme 4 shows a stepwise mechanism proposed from similar work by Ohwada et al.[16] In this case, *O*-protonated *aci*-nitro species generated in situ would undergo 1,3-dipolar cycloaddition. Further work is required to determine the real pathway to the isoxazole.

Time was less critical on the outcome of the 1,3-dipolar cycloaddition reaction. The optimal time would appear to be 5 minutes by the recorded UV % peak areas shown by LC-MS. However, as long as the optimal temperature was reached, a high yield of product was observed across the time ranges from 30 s to 20 min.

The optimal temperature was found to be 140 °C for forming the 7-ring fused isoxazole **2a**. It was also the case that 140 °C for 5 min was optimal for the formation of 6-ring fused isoxazole **2b** and the 5-ring fused isoxazole **2d** (Table 1).



Scheme 4. Plausible mechanism for the formation of compounds **2a**,**b**,**d**.

Further studies (Table 2) indicated that two equivalents of concentrated sulfuric acid (pK_a −3)[17] were the best combination of acid and equivalents for the successful cycloadditions. Concentrated hydrochloric acid (pK_a −8)[17] and TFA (pK_a 0.25)[17] gave considerable product peaks by LC-MS (UV %) but weaker acids such as acetic acid (pK_a 4.76)[17] and phosphoric acid (pKa 2.12)[17] resulted in little or no products with mainly starting material recovered. Interestingly, methanesulfonic acid (pK_a −0.6)[17] and trifluoromethanesulfonic acid (pK_a −14)[17] gave little product formation despite being strong acids.

It is clear that the stoichiometric involvement of 2 equiv of acid is optimal (Table 2). Too little acid prevents full consumption of all the starting materials, but with too much acid, increased by-product formation and decomposition were evident. The proposed mechanism in Scheme 4 is supportive of the use of two stoichiometric amounts of acid in order to achieve the isoxazole with an overall loss of water from the starting materials.

It was not possible to prepare the novel bicyclic 8-ring fused isoxazole from intermediate 2-nitro-1,1-ethenediamine **1c**. We propose that the greater 'degrees of freedom' within this system ($n = 4$) make it less likely to achieve the required conformation for cycloaddition, and in these cases, competing by-products are formed in preference, even with longer times and elevated temperatures only decomposition products were observed. It was also not possible to achieve intermolecular cycloaddition reactions with external sources of alkyne. We assume that the protonated 2-nitro-1,1-ethenediamine generated was prone to either intramolecular chemistry or decomposition before any external alkyne source can get close enough to react (Table 2).

When using the optimised conditions of acetonitrile for 5 min of microwave irradiation at 140 °C in the presence of 2 equiv of concentrated sulfuric acid, novel compounds **2a** and **2b** were isolated in high yield (79% and 83%, respectively).[18] The 5-ring fused isoxazole **2d** was isolated with good crude weight but after chromatography, only poor yields of clean material were recorded.[18]

In summary a novel synthesis of previously unreported fused bicyclic isoxazoles **2a** (79%), **2b** (83%) and **2d** (poor yield/stability) has been developed and the products characterised.[18] The optimal conditions for the intramolecular 1,3-dipolar cycloaddition reaction on intermediates **1a,b,d** are two equivalents of concentrated sulfuric acid in acetonitrile (0.2 mol/L) with microwave irradiation at 140 °C for 5 min.

This finding is a valuable addition to the literature of isoxazoles formed by the [3+2] cycloaddition reaction. Our derived 2-nitro-1,1-ethenediamines containing an intramolecular alkyne have formed a new class of bicyclic isoxazole systems of which very little is known. Moreover, this report forms a starting point for the synthesis of further novel heterocycles using similar methodology.

Table 2
The effects of acid and equivalents on the microwave-assisted synthesis of bicyclic isoxazoles **2a**,**b**,**d**

Substrate	Acid	Equivalents	Product[a] (UV %)
1a	H_2SO_4	2	**2a** (78)
1a	H_2SO_4	1	**2a** (67)
1a	H_2SO_4	0.5	**2a** (59)
1a	H_2SO_4	3	**2a** (72)
1a	H_2SO_4	5	**2a** (64)
1a	TFA	2	**2a** (69)
1a	HCl	2	**2a** (69)
1a	$MeSO_3H$	2	**2a** (1)
1a	$MeSO_3H$	4	No product
1a	CF_3SO_3H	2	**2a** (11)
1a	H_3PO_4	2	No product[b]
1a	AcOH	2	**2a** (10)
1a	AcOH	4	**2a** (6)
1b	H_2SO_4	2	**2b** (90)
1c	H_2SO_4	2	No product
1c	H_2SO_4	1	No product
1c[c]	H_2SO_4	2	No product
1c[d]	H_2SO_4	10	No product
1c[e]	H_2SO_4	2	No product
1d	H_2SO_4	2	**2d** (51)

Each reaction was conducted at 140 °C for 5 min in the microwave oven with MeCN as solvent.

[a] Results quoted as percentage area from the LC-MS UV trace.
[b] Poor solubility of the acid in the reaction mixture.
[c] Intermolecular reaction attempted with benzylethyne (5 equiv).
[d] Intermolecular reaction attempted with benzylethyne (4 equiv).
[e] Intermolecular reaction attempted with propynoic acid ethyl ester (5 equiv).

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15. Electrospray ionisation technique with quadrupole mass detector (Waters®, Acquity™). Formic acid generic analytic UPLC open access liquid chromatography mass spectra (LC-MS) 2 min method; LC conditions; The UPLC analysis was conducted on an Acquity UPLC BEH C18 column (50 × 2.1 mm id 1.7 μm packing diameter) at 40 °C, the solvents employed were A = 0.1% v/v solution of formic acid in H_2O and B = 0.1% v/v solution of formic acid in MeCN, the gradient employed was 0 min 97% A–3% B; 1.5 min 0% A–100% B; 1.9 min 0% A–100% B; 2.0 min 97% A–3% B, flow rate 1 ml/min, the UV detection was a summed signal from wavelength of 210 to 350 nm, MS conditions; MS Waters ZQ, Ionisation mode; alternative-scan positive and negative electrospray, Scan range; 100–1000 AMU, Scan time; 0.27 s, Inter scan delay 0.10 s.
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18. All reactions were performed with a Biotage initiator (2.5) in a sealed microwave reaction vessel. *General procedure for the synthesis of bicyclic isoxazoles*: To a suspension of nitro-etheneamine derivative (**1a–d**) (0.815 mmol) in MeCN (4 mL) was added concd H_2SO_4 (2 equiv) (1.63 mmol). The mixture was then submitted to microwave irradiation for 5 min at 140 °C. After cooling, the reaction solvent was evaporated in vacuo and the crude sample was purified by flash chromatography with a gradient of 100% CH_2Cl_2

to 10% (2 M NH_3 in MeOH) in CH_2Cl_2. Fractions containing clean product were evaporated in vacuo and the product was dried in a vacuum oven at 50 °C overnight.

N-Methyl-3-phenyl-5,6-dihydro-4*H*-isoxazolo[3,4-*c*]azepin-8-amine (**2a**): White solid, mp 113–115 °C (dec); LC-MS $[M+H]^+$ 242; HR-MS (ES+), calcd $[M+H]^+$ $C_{14}H_{16}N_3O$, 242.1293, found $[M+H]^+$ 242.1286; ^1H NMR (400 MHz, $CDCl_3$): δ 2.01–2.10 (m, 2H), 2.82–3.05 (m, 5H), 3.68–3.70 (m, 2H), 7.36–7.60 (m, 3H), 7.72–7.76 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.5, 27.7, 28.6, 47.9, 113.6, 126.7, 127.7, 129.0, 130.1, 151.8, 157.0, 166.1; IR (solid): ν 3393, 3056, 2896, 1634, 1526, 1448, 1208, 1162 cm^{-1} *N*-Methyl-3-phenyl-4,5-dihydroisoxazolo[3,4-*c*]pyridin-7-amine (**2b**): White solid, mp 145–147 °C (dec); LC-MS $[M+H]^+$ 228; HR-MS (ES+), calcd $[M+H]^+$ $C_{13}H_{14}N_3O$, 228.1137, found $[M+H]^+$ 228.1134; ^1H NMR (400 MHz, $CDCl_3$): δ 2.91 (t, J = 6.8 Hz, 2H), 2.99 (s, 3H), 3.78 (t, J = 6.7 Hz, 2H), 4.96–5.45 (br s, 1H NH), 7.38–7.63 (m, 3H), 7.75–7.79 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.8, 27.3, 46.1, 111.1, 126.0, 127.8, 129.1, 130.0, 149.8, 152.1, 163.2; IR (solid): ν 3204, 2944, 1642, 1613, 1555, 1449, 1166 cm^{-1}.

N-Methyl-3-phenyl-4*H*-pyrrolo[3,4-*c*]isoxazol-6-amine (**2d**): Pale brown solid, mp 76–78 °C (dec); LC-MS $[M+H]^+$ 214; HR-MS (ES+), calcd $[M+H]^+$ $C_{12}H_{12}N_3O$, 214.0980, found $[M+H]^+$ 214.0976; ^1H NMR (400 MHz, $CDCl_3$): δ 3.16 (s, 3H), 4.68 (s, 2H), 7.44–7.53 (m, 3H), 7.70–7.74 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.6, 49.7, 123.7, 126.3, 127.0, 129.2, 130.3, 155.0, 160.6, 167.8; IR (solid): ν 3253, 2931, 1744, 1621, 1488, 1450, 1411, 1166 cm^{-1}.