HETEROCYCLES, Vol. 84, No. 2, 2012, pp. 1013 - 1021. © 2012 The Japan Institute of Heterocyclic Chemistry
Received, 8th July, 2011, Accepted, 1st August, 2011, Published online, 11th August, 2011
DOI: 10.3987/COM-11-S(P)79

ALKYNE-ACETAL CYCLISATION REACTIONS MEDIATED BY FORMIC ACID; 3-ACYLATED-2,5-DIHYDROFURANS AND RELATED OXYGEN AND NITROGEN HETEROCYCLES

James D. Cuthbertson,[a] Andrew A. Godfrey,[b] William P. Unsworth,[a] and Richard J. K. Taylor[a*]

[a]Department of Chemistry, University of York, Heslington, York YO10 5DD, U.K. Tel: +44-(0)1904-322606; Fax: +44-(0)1904-324523; E-mail: richard.taylor@york.ac.uk

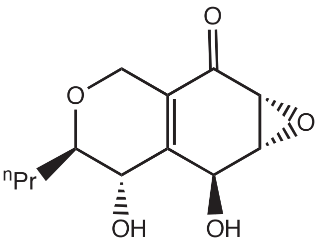
[b]AstraZeneca, Chemical Sciences, Pharmaceutical Development, Silk Road Business Park, Macclesfield, Cheshire, SK10 2NA, U.K.

Abstract – The utility of formic acid for the cyclisation of alkyne ω-acetals is described; the scope and limitations of this process are outlined and a range of acylated heterocyclic building blocks (2,5-dihydrofurans, 2,5-dihydro-1*H*-pyrroles, tetrahydropyridines, 2*H*-chromenes, 1,2-dihydroquinolines and benzoxepin-5(2*H*)-ones) are reported.

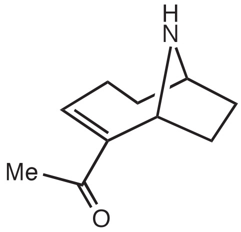
Dedicated to Professor Al Padwa to acknowledge his outstanding contributions to heterocyclic chemistry – and his friendship in the Lake District, in Istanbul, and in many other exotic locations!

INTRODUCTION

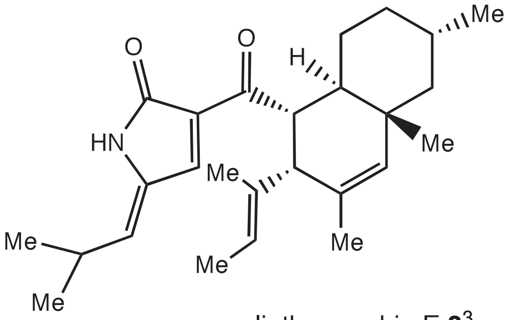
Partially reduced heterocycles bearing acyl substituents are valuable synthetic building blocks and are also found in biologically active natural products including cycloepoxydon (**1**), anatoxin A (**2**) and myceliothermophin E (**3**) (Figure 1).[1-3]



cycloepoxydon **1**[1]



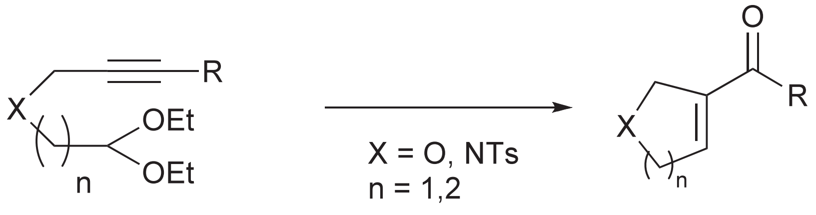
anatoxin A **2**[2]



myceliothermophin E **3**[3]

Figure 1

As part of a natural product synthesis programme,[4] we required ready access to a range of acylated dihydrofurans, dihydropyrroles, and higher homologues **5** of this type. Given our interest in tandem reactions,[4,5] we became attracted to approaches based on the cyclisation of ω-formyl alkynes which can be mediated by both Lewis and Brønsted acids.[6,7] As aliphatic aldehydes can be difficult to purify and prone to decomposition on storage, we explored the direct use of the corresponding alkyne ω-acetals **4** as cyclisation precursors (Scheme 1).[8]

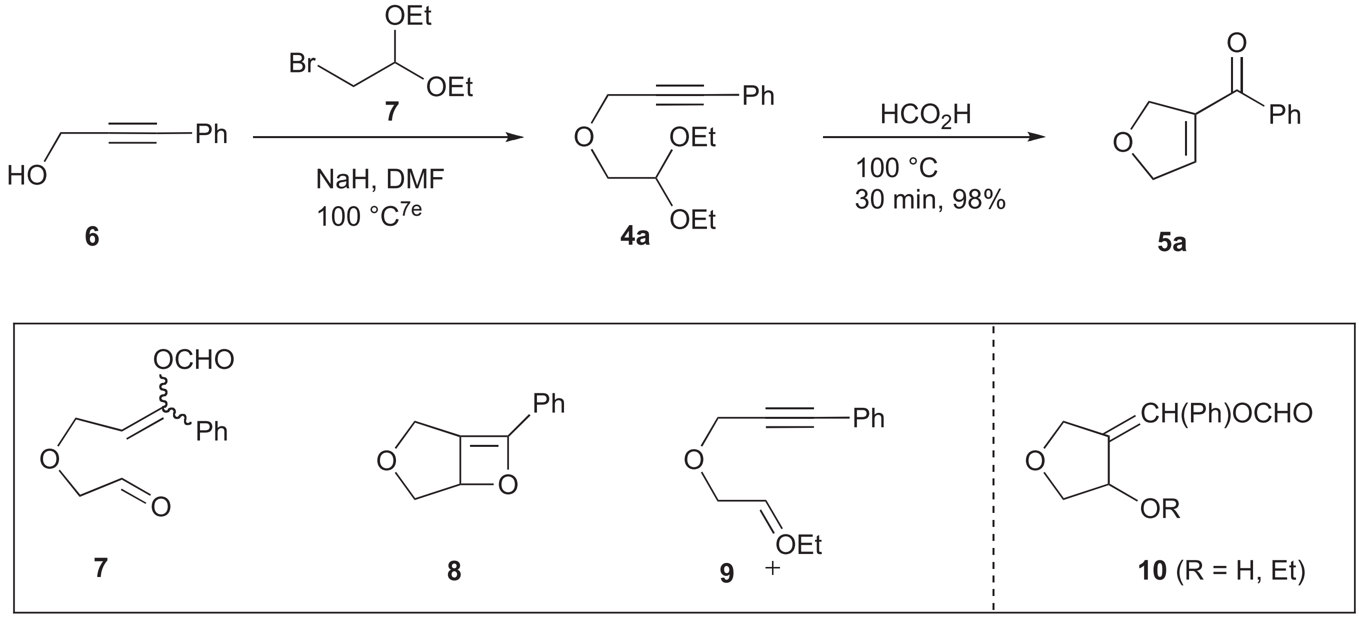


4 **5**

Scheme 1

RESULTS AND DISCUSSION

Initial studies were carried out using the known alkynyl acetal **4a**,[7e] which was readily prepared from alcohol **6** and commercially available acetal **7** using a modification of the published procedure (HMPA was omitted).[7e] When the acetal is prepared using this method, its direct use in the subsequent cyclisation reaction, removing the need to hydrolyse to the aldehyde, is obviously beneficial. A range of Lewis and Brønsted acids have been employed for alkyne cyclisations,[6,7] but our attention was taken by a report from Menashe and Shvo on the use of formic acid as an economical, metal-free method for the conversion of alkynes into carbonyl compounds.[9] We therefore explored the use of these formic acid conditions for the conversion of acetal **4a** into dihydrofuran **5a** (Scheme 2). We were delighted to observe that, on heating acetal **4a** in neat formic acid at 100 ºC, rapid conversion into dihydrofuran **5a** took place and, after purification, compound **5a** was isolated in 98% yield. The reaction was also found to proceed at lower temperatures, with a resulting increase in reaction time (*e.g*. rt, 24 h, 98%). The practicality of this procedure should be emphasised – on completion of the reaction, the formic acid can be simply removed *in vacuo* to give the product which can be used directly or further purified by chromatography.

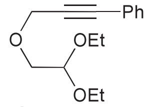
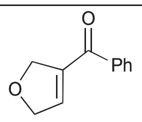
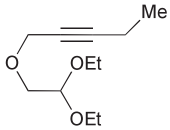
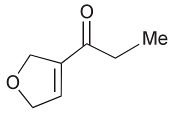
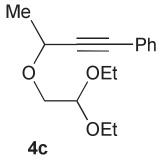
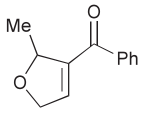
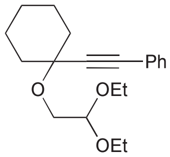
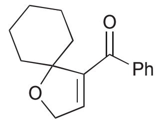
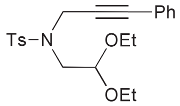
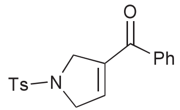
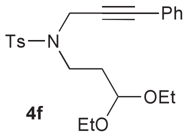
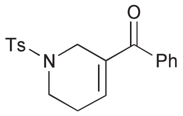
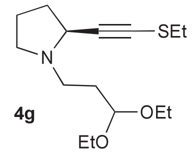
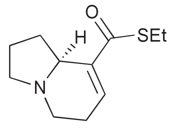


Scheme 2

Based on related studies, a number of mechanistic proposals could be considered, including: (i) initial addition of formic acid to the alkyne giving an intermediate **7** followed by an aldol-type condensation;[7d] (ii) proceeding by the intermediacy of an oxete **8**;[7a,7f,7g,10] (iii) a Prins-type cyclisation initiated by formation of oxonium ion **9**.[7e,g,h] We have not carried out a detailed mechanistic study on this process but when the reaction was carried at rt and stopped after ~30 min, potential intermediates tentatively assigned as enol formates **10** {*e.g*. for **10a**, HRMS (ESI): calcd. for $C_{12}H_{12}NaO_4$, 243.0628. Found: $[MNa]^+$, 243.0627 (0.1 ppm error); ^1H NMR, 8.14 ppm, OCHO} were isolated in addition to the expected product **5a**; this observation is in accord with the operation of a Prins-type process.

Having established conditions for the efficient cyclisation of acetal **4a**, we were in a position to investigate the scope of the transformation. Thus, a range of substrates **4b-4g** were prepared *via* alkylation of the corresponding propargylic alcohols or *N*-tosyl amines and subjected to the formic acid conditions (Table 1).

Table 1. Scope of formic acid-mediated cyclisation sequence[a]

Entry	**Substrate**	**Product**	**Yield**[b]
i	 **4a**	 **5a**	98%
ii	 **4b**	 **5b**	70%[c]
iii	 **4c**	 **5c**	80%[c]
iv	 **4d**	 **5d**	64%[c]
v	 **4e**	 **5e**	77%
vi	 **4f**	 **5f**	69%
vii	 **4g**	 **5g**	97%[d]

[a] All reactions were performed on a 0.25 mmol scale using formic acid (1 mL) at 100 °C for 30 min.

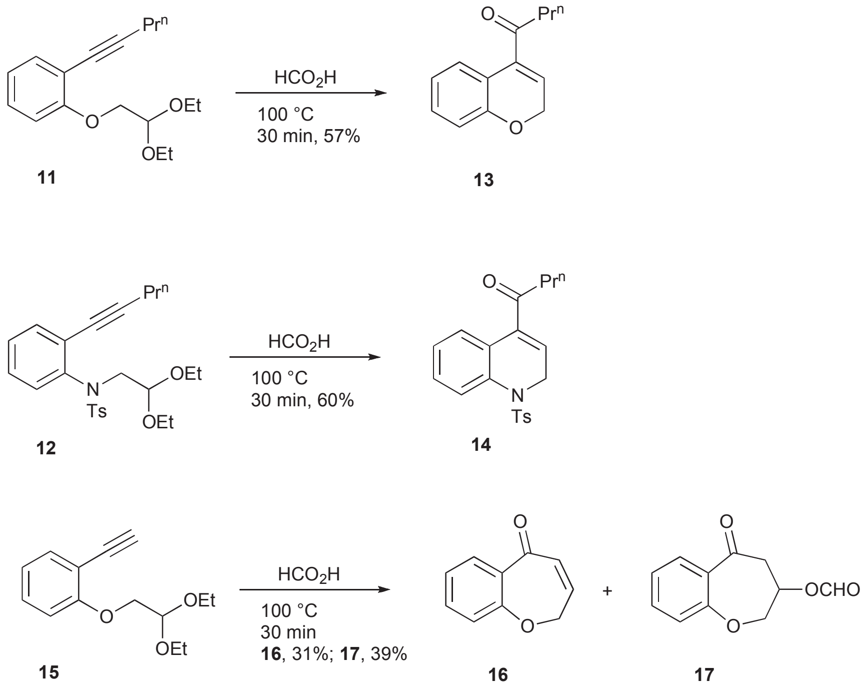
[b] Isolated yields after purification by column chromatography.

[c] Novel products.

[d] A reaction time of 2 h was employed.

As can be seen from Table 1, all of the substrates **4a-4g** were found to cyclise in moderate to excellent yield. In terms of dihydrofuran preparation, both aromatic and aliphatic alkyne substituents were tolerated (entries i-iv). The reaction was also found to be applicable to secondary and tertiary propargylic alcohols, which gave the methyl substituted dihydrofuran **5c** and the spirocyclic example **5d**, respectively. This methodology was equally applicable to the production of nitrogen heterocycles (entries v-vi); thus, *N*-Ts amine **4e** gave 2,5-dihydro-1*H*-pyrrole **5e**, and the higher homologue **4f** gave tetrahydropyridine **5f**. Finally (entry vii), an example is shown to illustrate that heteroatom-substituted alkynes are also compatible with this methodology.[4c] Alkyne **4g**, easily available from L-proline, was treated with formic acid under the standard conditions giving almost quantitative cyclisation to the bicyclic thioester **5g** {$[\alpha]_D$ −87 (c 0.97, $CHCl_3$)}. Such thioesters appear to be valuable synthetic building blocks and, indeed, thioester **5g** has recently been employed by our group to prepare (−)-grandisine B and (+)-grandisine D *via* a novel synthetic route.[4c]

In the final part of this study, we examined the cyclisation reactions of phenol- and aniline-derived substrates **11**, **12** and **15**. On subjection to the standard reaction conditions, the aromatic precursors **11** and **12** were converted into the novel chromene and 1,2-dihydroquinoline derivatives **13** and **14**, respectively, in reasonable yield. In all of the previous examples, cyclisation was observed at the proximal alkyne carbon atom but *endo*-cyclisation was seen when unsubstituted alkyne **15** was subjected to the reaction conditions. In this instance the known benzoxepinone derivative **16**[11] was isolated in 31% yield along with the formyl analogue **17** (39%; when re-subjected to the reaction conditions slow conversion of formate **17** into oxepine **16** was observed).



Scheme 3

In summary, a simple formic acid procedure has been developed for the conversion of alkyne ω-acetals directly into acyl heterocyclic building blocks. Preliminary studies into the scope and limitations of the methodology have been investigated and the sequence has been utilised to prepare 2,5-dihydrofurans, 3,6-dihydro-2*H*-pyrans, 2,5-dihydro-1*H*-pyrroles, tetrahydropyridines, 2*H*-chromenes, 1,2-dihydroquinolines and benzoxepin-5(2*H*)-ones. We are currently exploring the use of several of these compounds in natural product synthesis.

EXPERIMENTAL

NMR spectra were recorded on a Jeol ECX-400 instrument at 400 MHz (^{1}H) and 100 MHz (^{13}C); chemical shifts (δ) are quoted in parts per million (ppm) calibrated to residual non-deuterated solvent (^{1}H NMR: $CDCl_3$ at 7.26 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm). Coupling constants (*J*) are quoted in Hertz and are to the nearest 0.1 Hz. Infrared spectra were recorded on a ThermoNicolet IR100 spectrometer with NaCl plates. Low resolution electrospray ionisation (ESI) mass spectra were recorded on a Kratos MS 25 spectrometer. High resolution mass spectra were recorded on a Bruker MicrOTOF spectrometer. Melting points were recorded on Gallenkamp apparatus and are uncorrected. Thin layer chromatography was performed on aluminium plates coated with Merck Silica gel 60 F254 and flash column chromatography was carried out using Fluka flash silica gel 60 and the specified eluent. PE refers to the fraction of petroleum ether that boils in the range 40-60 °C. Cyclisation substrates **4a**,[7e] **4e**,[7e] **4f**,[7f] **4g**[4c] and 2-(pent-1-ynyl)aniline[12] were prepared using previously reported methods and other starting materials were prepared using related procedures. All other chemicals used in this study were commercially available and used as received.

Typical Alkyne-Acetal Cyclisation Procedure:

(2,5-Dihydrofuran-3-yl)(phenyl)methanone 5a: A stirred solution of alkyne **4a** (62 mg, 0.25 mmol) in formic acid (1 mL) was heated at 100 ºC (oil-bath pre-heated) for 30 min. The solution was cooled to rt and then concentrated *in vacuo* to afford the crude product which was purified by column chromatography (SiO_2, PE/EtOAc, 9:1) to give compound **5a** (43 mg, 98%) as a crystalline solid; mp. 67-69 ºC; R_f 0.23 (PE/EtOAc, 4:1) (other data fully consistent to published values[7a]).

All other products were prepared using the above procedure. Products **5e,**[7a] **5f,**[7f] **5g**[4c] and **16**[11] gave data fully consistent to published values. Data for novel products follow:

1-(2,5-Dihydrofuran-3-yl)propan-1-one 5b (22 mg, 70%); pale yellow oil; R_f 0.21 (PE/EtOAc, 4:1); IR (neat) 2855, 1738, 1124, 1074 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (t, *J* = 7.3 Hz, 3H), 2.72 (q, *J* = 7.3 Hz, 2H), 4.80-4.88 (m, 4H), 6.71-6.74 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.9 (CH_3), 32.7 (CH_2), 74.4 (CH_2), 76.3 (CH_2), 136.3 (CH), 141.0 (C), 197.0 (C); *m/z* (ESI) 127 $[MH]^+$; [HRMS (ESI): calcd. for $C_7H_{11}O_2$, 127.0754. Found: $[MH]^+$, 127.0757 (2.7 ppm error)].

(2-Methyl-2,5-dihydrofuran-3-yl)(phenyl)methanone 5c: purified by column chromatography (SiO_2, PE/EtOAc, 9:1) as a pale yellow oil (38 mg, 80%); R_f 0.33 (PE/EtOAc, 4:1); IR (neat) 2973, 2848, 1644, 1359, 1276, 1240, 1084 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (d, *J* = 6.3 Hz, 3H), 4.77 (ddd, *J* = 16.1, 4.9, 1.9 Hz, 1H), 4.93 (ddd, *J* = 16.1, 5.6, 1.9 Hz, 1H), 5.30-5.38 (m, 1H), 6.54-6.56 (m, 1H), 7.44-7.49 (m, 2H), 7.54-7.60 (m, 1H), 7.77-7.81 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5 (CH_3), 74.5 (CH_2), 82.2 (CH), 128.4 (2 × CH), 128.8 (2 × CH), 132.6 (CH), 138.2 (C), 139.5 (CH), 143.5 (C), 191.4 (C); *m/z* (ESI) 189 $[MH]^+$; [HRMS (ESI): calcd. for $C_{12}H_{13}O_2$, 189.0910. Found: $[MH]^+$, 189.0912 (1.2 ppm error)].

1-Oxaspiro[4.5]dec-3-en-4-yl(phenyl)methanone 5d: purified by column chromatography (SiO_2, PE/EtOAc, 19:1 to 9:1) as a yellow oil (39 mg, 64%); R_f 0.49 (PE/EtOAc, 4:1); IR (neat) 2929, 1646, 1317, 1240, 1089 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23-1.36 (m, 1H), 1.61-1.76 (m, 7H), 2.00-2.11 (m, 2H), 4.75 (d, *J* = 1.9 Hz, 2H), 6.45 (t, *J* = 1.9 Hz, 1H), 7.42-7.47 (m, 2H), 7.53-7.58 (m, 1H), 7.73-7.77 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.3 (2 × CH_2), 25.0 (CH_2), 34.1 (2 × CH_2), 71.9 (CH_2), 90.4 (C), 128.3 (2 × CH), 128.9 (2 × CH_2), 132.4 (CH), 139.1 (C), 139.9 (CH), 145.5 (C), 192.4 (C); *m/z* (ESI) 265 $[MNa]^+$; [HRMS (ESI): calcd. for $C_{16}H_{18}NaO_2$, 265.1199. Found: $[MNa]^+$, 265.1192 (2.5 ppm error)].

1-(2*H*-Chromen-4-yl)butan-1-one 13: purified by column chromatography (SiO_2, PE/EtOAc, 9:1) as a yellow oil (29 mg, 57%); R_f 0.48 (PE/EtOAc, 4:1); IR (neat) 2964, 1682, 1485, 1456, 1226 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, *J* = 7.4 Hz, 3H), 1.72 (qt, *J* = 7.4, 7.3 Hz, 2H), 2.75 (t, *J* = 7.3 Hz, 2H), 4.82 (d, *J* = 4.1 Hz, 2H), 6.56 (t, *J* = 4.1 Hz, 1H), 6.87 (dd, *J* = 8.0, 1.3 Hz, 1H), 6.95 (ddd, *J* = 7.8, 7.6, 1.3 Hz, 1H), 7.18 (ddd, *J* = 8.0, 7.6, 1.6 Hz, 1H), 7.75 (dd, *J* = 7.8, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8 (CH_3), 17.9 (CH_2), 41.6 (CH_2), 64.3 (CH_2), 116.3 (CH), 119.7 (C), 121.6 (CH), 126.6 (CH), 128.9 (CH), 129.8 (CH), 135.1 (C), 154.3 (C), 200.7 (C); *m/z* (ESI) 225 $[MNa]^+$; [HRMS (ESI): calcd. for $C_{13}H_{14}NaO_2$, 225.0886. Found: $[MNa]^+$, 225.0890 (1.8 ppm error)].

1-{1-[(4-Methylphenyl)sulfonyl]-1,2-dihydroquinolin-4-yl}butan-1-one 14: purified by column chromatography (SiO_2, PE/EtOAc, 9:1) as a yellow oil (54 mg, 60%); R_f 0.33 (PE/EtOAc, 4:1); IR (neat) 2964, 1683, 1354, 1165, 1089 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (t, *J* = 7.4 Hz, 3H), 1.47 (qt, *J* = 7.4, 7.3 Hz, 2H), 2.24 (t, *J* = 7.3 Hz, 2H), 2.30 (s, 3H), 4.47 (d, *J* = 4.6 Hz, 2H), 6.24 (t, *J* = 4.6 Hz, 1H), 7.08 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 8.3 Hz, 2H), 7.25-7.30 (m, 1H), 7.37 (ddd, *J* = 7.8, 7.7, 1.6 Hz, 1H), 7.61 (d, *J* = 7.8, 1.4, 1H), 7.73 (dd, *J* = 8.1, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7 (CH_3), 17.5 (CH_2), 21.4 (CH_3), 41.2 (CH_2), 44.8 (CH_2), 126.7 (CH), 126.8 (C), 126.9 (CH), 127.2 (2 × CH), 127.7

(CH), 128.9 (CH), 129.3 (2 × CH), 130.7 (CH), 135.6 (C), 136.1 (C), 136.5 (C), 143.7 (C), 199.7 (C); *m/z* (ESI) 356 [MH]$^+$; [HRMS (ESI): calcd. for $C_{20}H_{22}NO_3S$, 356.1315. Found: [MH]$^+$, 356.1313 (0.6 ppm error)].

5-Oxo-2,3,4,5-tetrahydrobenzo[b]oxepin-3-yl formate 17: purified by column chromatography (SiO_2, PE/Et_2O, 20:1 to 10:1) as a colourless crystalline solid (15 mg 39%); mp 60-62 °C; R_f 0.19 (PE/Et_2O, 4:1); IR (thin film) 3429, 1718, 1653, 1475, 1302, 1165, 1108, 1012 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.21 (dd, *J* = 12.3, 7.5 Hz, 1H), 3.28 (dd, *J* = 12.3, 6.0 Hz, 1H), 4.28-4.37 (m, 2H), 5.52-5.58 (m, 1H), 7.11-7.16 (m, 2H), 7.44-7.48 (m, 1H), 7.84 (dd, *J* = 7.9, 1.8, 1H), 8.06 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 46.2 (CH_2), 76.1 (CH), 76.7 (CH_2), 120.7 (CH), 123.4 (CH), 127.8 (C), 129.8 (CH), 134.4 (CH), 159.9 (CH), 162.8 (C), 194.7 (C);); *m/z* (ESI) 229 [MNa]$^+$; [HRMS (ESI): calcd. for $C_{11}H_{10}NaO_4$, 229.0471. Found: [MNa]$^+$, 229.0470 (1.8 ppm error)].

ACKNOWLEDGEMENTS

The authors would like to thank the EPSRC and AstraZeneca for studentship support (J.D.C) and the EPSRC for postdoctoral support (W.P.U., EP/G068313/1).

REFERENCES AND NOTES

1. A. Gehrt, G. Erkel, T. Anke, and O. Sterner, *J. Antibiot.,* 1998, **51**, 455.
2. J. P. Devlin, O. E. Edwards, P. R. Gorham, N. R. Hunter, R. K. Pike, and B. Stavric, *Can. J. Chem.,* 1977, **55**, 1367.
3. Y.-L. Yang, C.-P. Lu, M.-Y. Chen, K.-Y. Chen, Y.-C. Wu, and S.-H. Wu, *Chem. Eur. J.*, 2007, **13**, 6985.
4. (a) J. D. Cuthbertson, A. A. Godfrey, and R. J. K. Taylor, *Synlett,* 2010, 2805; (b) J. D. Cuthbertson, A. A. Godfrey, and R. J. K. Taylor, *Tetrahedron Lett.*, 2011, **52**, 2024; (c) J. D. Cuthbertson, A. A. Godfrey, and R. J. K. Taylor, *Org. Lett.*, 2011, **13**, 3976.
5. R. J. K. Taylor, M. Reid, J. Foot, and S. A. Raw, *Acc. Chem. Res.,* 2005, **38***,* 851; A. R. Burns, G. D. McAllister, S. E. Shanahan, and R. J. K. Taylor, *Angew. Chem. Int. Ed.,* 2010*,* **49**, 5574 and references therein.
6. For the pioneering research on ω-carbonyl alkyne cyclisations see: (a) C. E. Harding and M. Hanack, *Tetrahedron Lett.,* 1971, **12**, 1253; (b) R. J. Balf, B. Rao, and L. Weiler, *Can. J. Chem.,* 1971, **49**, 3135.
7. For recent research on ω-carbonyl alkyne cyclisations see: (a) J. U. Rhee and M. J. Krische, *Org.*

Lett., 2005, **7**, 2493; (b) T. Jin and Y. Yamamoto, *Org. Lett*., 2007, **9**, 5259; (c) A. Saito, M. Umakoshi, N. Yagyu, and Y. Hanzawa, *Org. Lett.,* 2008, **10**, 1783; (d) C. González-Rodríguez, L. Escalante, J. A. Varela, L. Castedo, and C. Saá, *Org. Lett.,* 2009, **11**, 1531; (e) T. Xu, Z. Yu, and L. Wang, *Org. Lett.,* 2009, **11**, 2113; (f) T. Jin, F. Yang, C. Liu, and Y. Yamamoto, *Chem. Commun*., 2009, 3533; (g) T. Xu, Q. Yang, Z. Yu, D. Li, J. Dong, and Y. Li, *Chem. Eur. J*., 2010, **16**, 9264; (h) D. Zheng, W. Gong, Z. Ma, B. Ma, X. Zhao, Z. Xie, and Y. Li, *Tetrahedron Lett*., 2011, **52**, 314 and references therein.

8. To the best of our knowledge, there are only two reports of the use of alkyne-acetals in a Brønsted acid mediated cyclisation (reference 7d, footnote 8 and reference 7f).
9. N. Menashe and Y. Shvo, *J. Org. Chem.,* 1993, **58**, 7434.
10. C. E. Harding and S. L. King, *J. Org. Chem.,* 1992, **57**, 883.
11. S.-R. Li, H.-M. Chen, L.-Y. Chen, J.-C. Tsai, P.-Y. Chen, S. C.-N. Hsu, and E.-C. Wang, *ARKIVOC*, **2008**, (ii), 172.
12. L. F. Kuyper, D. P. Baccanari, M. L. Jones, R. N. Hunter, R. L. Tansik, S. S. Joyner, C. M. Boytos, S. K. Rudolph, V. Knick, H. R. Wilson, J. M. Caddell, H. S. Friedman, J. C. W. Comley, and J. N. Stables, *J. Med. Chem*., 1996, **392**, 892.