Facile synthesis of fused quinolines via intramolecular Friedel–Crafts acylation

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The intramolecular cyclisation of 6-[(phenoxy/phenylthio)methyl][1,3]dioxolo[4,5-*g*]quinoline-7-carboxylic acids to [1]benzoxepino[3,4-*b*][1,3]dioxolo[4,5-*g*]quinolin-12(6*H*)-ones and [1]benzothiepino[3,4-*b*][1,3]dioxolo[4,5-*g*]quinolin-12(6*H*)-ones in the presence of Eaton's reagent (P_2O_5-$MeSO_3H$) is described. This cyclisation protocol requires milder conditions than those traditionally employed and is characterised by relatively low reaction temperatures and ease of product isolation.

Keywords: Friedel–Crafts reactions, cyclisation, fused 1-benzoxepins, 1-benzothiepins, quinolines, Eaton's reagent

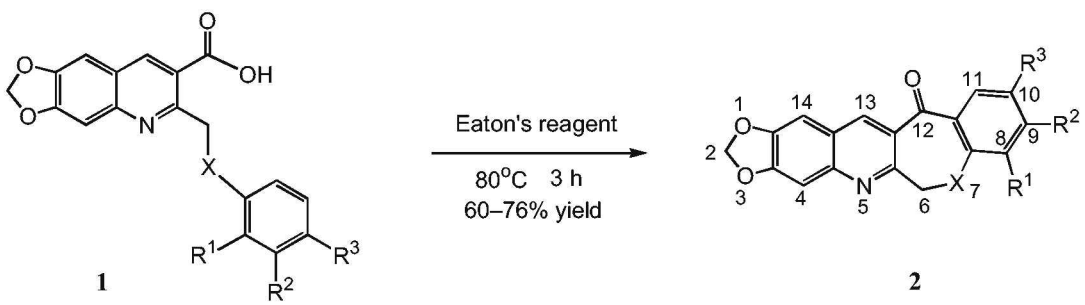
Quinoline-fused ring systems are the back-bone of many natural products and pharmacologically significant compounds and they display a broad range of biological activity.[1-3] For example, the anticancer alkaloid camptothecin and related compounds are important anticancer and antiviral alkaloids and several analogues are used as pharmaceuticals.[4,5]

Because of the interest in these findings, quinoline-fused compounds have been popular targets of synthesis, and a wide variety of protocols have been used. For instance, syntheses have included Friedländer condensation reactions,[6] radical cyclisation[7] and intramolecular Friedel–Crafts acylation reactions.[8] Gao[8] and Yang[9] respectively reported the synthesis of benzothiepinoquinolinones and benzoxepinoquinolinones *via* intramolecular Friedel–Crafts acylations of phenylsulfanylmethyl- and phenoxymethyl-substituted quinolinic acids. The intramolecular Friedel–Crafts acylation of arylcarboxylic acids is an important route to the preparation of cyclic aromatic ketones. Conventionally, Friedel–Crafts acylation can be achieved by treating the aryl acids with a variety of condensing agents including liquid HF, H_2SO_4, $TiCl_4$, $AlCl_3$, and $AlCl_3$/NaCl.[10] However, using these reagents, not only do the harsh reaction conditions make synthesis and product isolation difficult, but also a quantity of acidic waste is inevitably produced which leads to pollution problems after the reaction. Alternatively, polyphosphoric acid (PPA) can be used for similar cyclisations; however, its high viscosity and high reaction temperatures required make it difficult to handle for large-scale operations. It is clear that a more efficient protocol is needed. Recently, the inexpensive and commercially available Eaton's reagent, a mixture of P_2O_5 and $MeSO_3H$, has been widely used for effecting intramolecular cyclisations under mild conditions.[11] A number of interesting examples of intramolecular Friedel–Crafts acylation using Eaton's reagent have been published, including the syntheses of quinolone heterocycles,[12] 4-hydroxycoumarins[13] and aromatic poly (ether ketone)s.[14]

In this paper, we report the synthesis of novel pentacyclic quinoline-fused compounds [1]benzoxepino[3,4-*b*][1,3]dioxolo[4,5-*g*]quinolin-14(6*H*)-ones and [1]benzothiepino[3,4-*b*][1,3]dioxolo[4,5-*g*]quinolin-14(6*H*)-ones **2a–e** using Eaton's reagent as condensing agent and solvent *via* the intramolecular cyclisation of 6-[(phenoxy/phenylthio)methyl][1,3]dioxolo[4,5-g]quinoline-7-carboxylic acids **1a–e** (Scheme 1).

Our initial efforts at cyclising **1a** employed PPA. The cyclisation could be achieved at 140 °C; however, only 20% of the product was isolated. Given the difficulties, we sought to identify alternative conditions. Accordingly, a variety of other reagents, *e.g.* H_2SO_4, *p*-TsOH, $TiCl_4$, and P_2O_5 were examined, each giving unacceptably poor yields of **2a.** We then tried Eaton's reagent, a mixture of P_2O_5 and $MeSO_3H$. We were pleased to discover that simply dissolving **1a** in Eaton's reagent and heating to only 80 °C resulted in conversion into **2a** in 65% yield within 3 h. The ease of isolation of **2a** was notable; a simple quench into a basic solution precipitates the product in acceptable purity (94%). The role of P_2O_5 in the reagent mixture P_2O_5/$MeSO_3H$ is as a drying agent. Addition of P_2O_5 decreases the strength of the sulfonic acid. A small amount of water resulting from the cyclisation reactions produces a decrease in acidity of $MeSO_3H$ but has little effect on the acid strength of $MeSO_3H$–P_2O_5 acid mixture. Phosphorus pentoxide is thus able to delay the deactivation by the water from the cyclisation. In neat $MeSO_3H$ substrate **1a** does not give cyclised product after heating at 80 °C over 10 h.

Encouraged by the successful synthesis of compound **2a**, we tested this protocol for the intramolecular cyclisation of other substrates **1b–e**. It was found that the method was effective



1

1a, 2a: X=O, R^1=CH_3, R^2=H, R^3=H
1b, 2b: X=S, R^1=H, R^2=H, R^3=H

2

1c, 2c: X=S, R^1=H, R^2=H, R^3=CH_3
1d, 2d: X=O, R^1=H, R^2=OCH_3, R^3=H
1e, 2e: X=O, R^1=H, R^2=H, R^3=Cl

Scheme 1

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Table 1 Melting points, yields and element analysis data of compounds **2a–e**

Compd	Mol. formula	M.p./°C	Yield/%	Elemental analysis/% found (calcd)		
				C	H	N
2a	$C_{19}H_{13}NO_4$	194–195	69	71.59 (71.47)	4.25 (4.10)	4.18 (4.39)
2b	$C_{18}H_{11}NO_3S$	188–189	76	67.15 (67.28)	3.22 (3.45)	4.53 (4.36)
2c	$C_{19}H_{13}NO_3S$	203–205	70	68.18 (68.04)	3.97 (3.91)	4.01 (4.08)
2d	$C_{19}H_{13}NO_5$	199–201	63	67.92 (68.06)	4.01 (3.91)	4.12 (4.08)
2e	$C_{18}H_{10}ClNO_4$	179–181	60	63.92 (63.64)	2.89 (2.97)	4.22 (4.12)

Table 2 ^{1}H NMR and IR data of compounds **2a–e**

Compd	IR, ν/cm^{-1}	^{1}H NMR, δ
2a	1637 (C=O) 1253 (C–O)	2.30 (s,3H, 4-CH_3), 5.44 (2H, s, 6-CH_2), 6.25 (2H, s, 10-CH_2), 7.12 (1H, m, H-2), 7.46 (1H, m, H-3), 7.66 (1H, m, H-1), 7.97 (1H, d, *J* = 6.5 Hz, H-8), 8.07 (1H, m, H-12), 8.67 (1H, s, H-13)
2b	1638 (C=O) 695 (C–S)	4.33 (2H, s, 6-CH_2), 6.14 (2H, s, 10-CH_2), 7.11-7.20 (2H, m, H-2,3), 7.55 (1H, m, H-4), 7.68 (1H, m, H-1), 8.01 (1H, m, H-8), 8.15 (1H, d, *J* = 6.9 Hz, H-12), 8.35 (1H, s, H-13)
2c	1636 (C=O) 751 (C–S)	2.40 (3H, s, 2-CH_3), 4.44 (2H, s, 6-CH_2), 6.17 (2H, s, 10-CH_2), 7.15 (1H, d, *J* = 6.3 Hz, H-3), 7.31 (2H, m, H-1,4), 7.51 (1H, m, H-8), 8.13 (1H, m, H-12), 8.46 (1H, s, H-13)
2d	1644 (C=O)	3.75 (3H, s, 3-OCH_3), 5.49 (2H, s, 6-CH_2), 6.25 (2H, s, 10-CH_2), 7.09 (1H, m, H-2), 7.32 (2H, m, H-1,4), 7.97 (1H, d, *J* = 6.5 Hz, H-8), 8.13 (1H, m, H-12), 8.75 (1H, s, H-13)
2e	1647 (C=O) 1279 (C–O)	5.57 (2H, s, 6-CH_2), 6.30 (2H, s, 10-CH_2), 7.15 (1H, m, H-3), 7.47 (2H, m, H-1,4), 8.05 (1H, d, *J* = 6.5 Hz, H-8), 8.14 (1H, m, H-12), 8.74 (1H, s, H-13)

for the cyclisation of these compounds with different types of substituents. In all cases, Eaton's reagent promoted cyclisation at 80 °C and gave high yields of compounds **2** within 3 h. As far as the amount of Eaton's reagent used is concerned, 5 ml Eaton's reagent to 1 mmol of substrate offered the desired product in the highest yield; more reagent did not improve the yield further.

Experimental

The melting points were determined by using WRS-1B melting points apparatus. ^{1}H NMR was measured with a Varian Inova 400 NMR spectrometer at 400 MHz. The reported chemical shifts were against TMS. Elemental analysis was performed using an Elementar Vario EL-III element analyser.

The starting materials 6-[(phenoxy/phenylthio)methyl][1,3] dioxolo[4,5-g]quinoline-7-carboxylic acids **1a–e** were prepared according to described procedures.[15]

[1]Benzoxepino[3,4-b][1,3]dioxolo[4,5-g]quinolin-14(6H)-ones and [1]benzothiepino[3,4-b][1,3]dioxolo[4,5-g]quinolin-14(6H)-ones **2a–e**, *general procedure*

6-[(Phenoxy/phenylthio)methyl][1,3] dioxolo[4,5-g]quinoline-7-carboxylic acids **1a–e** (1 mmol) and Eaton's reagent[11] (3 ml) were added to a 10 ml round flask and stirred at 80 °C for 3 h. Then the reaction mixture was poured into ice-cold saturated aqueous sodium carbonate. The crude product was obtained after filtration and washing with water. The pure products were obtained by recrystallisation from ethanol to give the [1]benzoxepino[3,4-*b*][1,3]dioxolo[4,5-*g*] quinolin-14(6*H*)-ones (**2a,d,e**) and [1]benzothiepino[3,4-*b*][1,3] dioxolo[4,5-*g*]quinolin-14(6*H*)-ones (**2b,c**). The melting points, yields, and elemental analysis of compounds **2a–e** are summarised in Table 1, and their IR and ^{1}H NMR data are listed in Table 2.

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