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A new and convenient approach to heterotetracyclic benzoxazocines through addition of 1,3-dicarbonyl compounds to quinolinium salts

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ABSTRACT

The synthesis of a series of benzoxazocines has been achieved in good yields by tandem *C*-alkylation and intramolecular O-alkylation of 1,3-dicarbonyl compounds with quinolinium salts. This is a novel example of the synthesis of eight-membered rings via a tandem process, which provides a method for the synthesis of medium-ring heterocycles.

The complexity and diversity of nitrogen- and oxygen-containing heterocycles within alkaloids make them interesting compounds.[1] Tetrahydroquinolines constitute an important class of organic compounds. Their fused analogues have found considerable utility as pharmaceutical agents demonstrating inhibition of the cholesterol ester transfer protein and antiallergenic, antiinflammatory, antiviral, antimalarial and antihypertensive activities.[2] On the other hand, polycyclic frameworks lead to relatively rigid structures that might be expected to show substantial selectivity in their interactions with enzymes or receptors.[3]

The synthesis of medium-ring heterocycles with a ring size in the range of 7–11 has received much attention in organic chemistry due to their presence in natural products and wide applications as drug candidates and in catalysis.[4] Among them, benzoxazepines show promising pharmacological activity including antidepressant, antithrombotic and antipsychotic along with the activity against breast cancer.[5] However, limited attention has been given to the synthesis of medium-ring heterocycles, examples include cycloadditions, ring closing metathesis, ring expansion, Mitsunobu reactions and metal-mediated ring cyclization.[6] Therefore, the development of methods to generate medium-ring systems that contain nitrogen and oxygen for applications in natural product or non-natural compound synthesis is a useful aim. Tandem reactions (TRs) which result from the combination of multiple transformations in one pot are highly efficient tools for the synthesis of complex compounds. Over the past few years, there has been a tremendous development in TRs affording novel chemical compounds for drug discovery efforts.[7]

Addition of nucleophilic reagents to quinolinium salts has proved to be a useful method for the synthesis of substituted quinoline derivatives.[8] The preparation of bioactive heteroatom-containing heterocycles is one of our ongoing projects due to their interesting bio-activities.[9] We earlier demonstrated an efficient synthesis of novel indole-annulated pentacyclic indolylhydroquinoline[9a] and indolyl-tetrahydroisoquinoline skeletons[9b] via addition of indolin-2-thiones, as bifunctional nucleophiles, to quinolinium and isoquinolinium salts. This protocol is a very mild and simple method for the construction of eight-membered rings in fused heterocycles in a one-step process. We herein report an unprecedented C-alkylation/intramolecular O-alkylation tandem process for the construction of heterotetracyclic benzoxazocines (Scheme 1) of which analogues are widely distributed in biologically interesting natural products[4i–k] and synthetic molecules.

To achieve the optimal reaction conditions for the tandem synthesis of benzoxazocines, we initially investigated the effects of solvent and base on the reaction of *N*-methylquinolinium salt **2** and 5,5-dimethylcyclohexane-1,3-dione as a simple model reaction. In the absence of base, none of the desired product was obtained, while good results were obtained in the presence of K_2CO_3 after 4 h. The effect of solvent was studied using toluene, CH_3CN and H_2O, with acetonitrile providing the highest yield and shortest reaction time.

The IR spectrum of **3a** exhibited peaks at 2953 cm^{-1} and 1606 cm^{-1} for the unsaturated carbonyl function. The ^1H NMR spectrum of **3a** showed two singlets (δ 0.99 and 1.08) for the methyl protons, two resonances (δ 1.98 and 2.02) for the geminal aliphatic methylene protons of the hydroquinoline ring, two signals (δ 2.16 and 2.20) for the allylic methylene protons and two resonances (δ 2.23 and 2.30) for the methylene protons α to the carbonyl, which are diastereotopic. A singlet for the N–CH_3 group (δ 3.20), a multiplet for the deshielded benzylic proton (δ 4.14–4.15) and a multiplet for the N–C*H*–O hydrogen (δ 5.54–5.55) were also observed. When the 2-methylquinolinium salt was used as a starting material, the signal at δ 5.54 was absent, and instead a signal at δ 1.82 for the methyl group was observed (see ^1H NMR of **3h**

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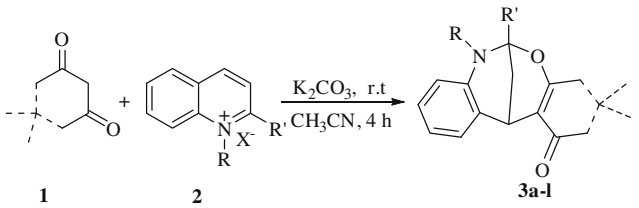


R = Me, Et, Bn, allyl, propargyl,
p-$BrC_6H_4CH_2$, CH_2CO_2Et
R' = H, Me
X = Br, I

Scheme 1. Synthesis of benzoxazocines.

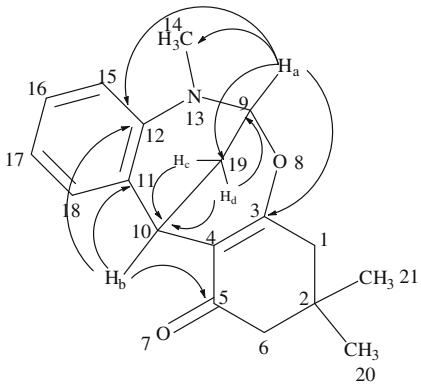
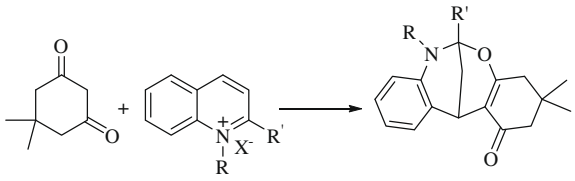


Figure 1. The key HMBC correlations in compound **3a**.

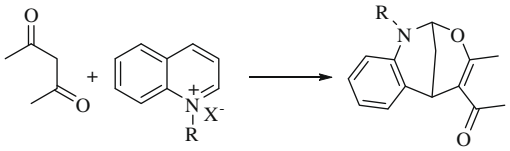
Table 1
Synthesis of 5,5-dimethylcyclohexane-1,3-dione-annulated benzoxazocines



Entry	R	R′	Product	Yield[a] (%)
1	Me	H	**3a**	83
2	Et	H	**3b**	81
3	Bn	H	**3c**	78
4	*p*-$BrC_6H_4CH_2$	H	**3d**	76
5	Allyl	H	**3e**	71
6	Propargyl	H	**3f**	68
7	CH_2CO_2Et	H	**3g**	70
8	Me	Me	**3h**	61

[a] Isolated yield.

Table 2
Synthesis of pentane-2,4-dione-annulated benzoxazocines



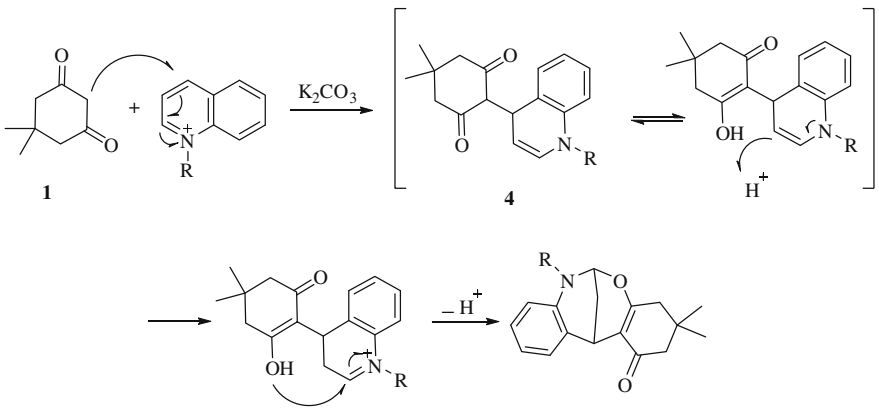
Entry	R	Product	Yield[a] (%)
1	Me	**3i**	47
2	Et	**3j**	45
3	Bn	**3k**	42
4	Allyl	**3l**	41

[a] Isolated yield.

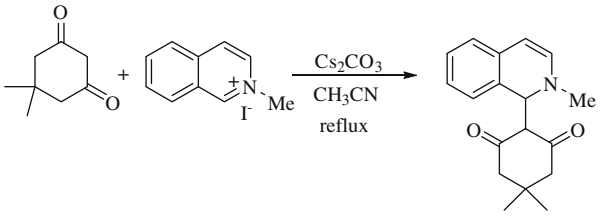
and Table 1). The ^{1}H-decoupled ^{13}C NMR spectrum of **3a** showed 18 distinct resonances in agreement with the proposed structure. The ^{13}C DEPT experiment showed resonances at δ 25.8 for the benzylic carbon (C-10), δ 26.2 readily recognized as the methylene carbon (C-19), two resonances at δ 27.7 and 29.9 (aliphatic methyl carbons), δ 37.5 (N–Me), two resonances at δ 42.5 and 50.9 (C-1 and C-6, respectively), δ 86.5 (C-9), four distinct resonances for the aromatic methine carbons, δ 168.8 (C–O), δ 196.3 (C=O) and three other quaternary carbons. Further evidence for the bridged structure was provided by the HMBC spectrum. The key correlations between H_a at δ 5.54 and the carbons at δ 168.8 (C-3) and 26.2 (C-19) implied that the connection points between the 5,5-dimethylcyclohexane-1,3-dione ring and the tetrahydro-quinoline ring were at C-9 and C-10. Some of the key HMBC correlations are shown in Figure 1.

To generalize this methodology, we reacted a series of other *N*-alkylquinolinium salts **2** to give the corresponding benzoxazocines under the optimized reaction conditions (Table 1). The reactions proceeded cleanly under mild conditions at room temperature, and no undesirable side reactions were observed to take place. The same configuration was assumed for the other derivatives on account of their spectroscopic similarities. This chemoselective outcome is in agreement with the results observed in previous nucleophilic substitutions of compounds **2**.[9a]

We next examined the substrate scope by reaction between *N*-alkylquinolinium salts **2** and pentane-2,4-dione. The reaction worked well and the yields of products were satisfactory (Table 2).



Scheme 2. Proposed mechanism for the formation of compounds **3**.



Scheme 3. Reaction of 5,5-dimethylcyclohexane-1,3-dione with *N*-methylisoquinolinium salt.

A plausible mechanism for the formation of the products is shown in Scheme 2. 5,5-Dimethylcyclohexane-1,3-dione (**1**) undergoes C-alkylation by attack at C-4 of quinolinium salt **2**. This leads to the formation of an enamine on the pyridine ring of the quinoline, which is protonated to form an iminium ion. Finally, intramolecular nucleophilic cyclization involving the hydroxy group gives the product.

We next investigated the addition of 5,5-dimethyl cyclohexane-1,3-dione to an *N*-methylisoquinolinium salt as the starting material, but the reaction failed to produce the desired product under the optimized conditions. Only the nucleophilic addition of 5,5-dimethylcyclohexane-1,3-dione was observed under heating and using Cs_2CO_3 as a stronger base (Scheme 3).

In conclusion, we have described a novel and highly efficient method for the synthesis of benzoxazocines. The present procedure has advantages of high yields, good functional group tolerance, high selectivity and mild reaction conditions. The starting materials are easily accessible making this procedure attractive for the preparation of benzoxazocines in a single step.[10]

Acknowledgement

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10. *General procedure for the synthesis of benzoxazocines* **3a–l**: A mixture of a 1,3-dione **1** (1 mmol), quinolinium salt **2** (1 mmol) and K_2CO_3 (0.14 g, 1 mmol) in CH_3CN (5 mL) was stirred at room temperature for 4 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure and the residue was separated by flash column chromatography on silica gel with petroleum ether/EtOAc (2:1) as eluent to afford the pure product.
Analytical data for selected products: 3,3,7-trimethyl-2,3,4,6,7,12-hexahydro-1*H*-6,12-methanodibenzo[*d*,*g*][1,3] oxazocin-1-one (**3a**); mp: 128–130 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.99 (s, 3H), 1.08 (s, 3H), 1.95–2.04 (m, 2H), 2.16 (ABd, *J* = 17.5 Hz, 1H), 2.20 (ABd, *J* = 17.5 Hz, 1H), 2.23 (ABd, *J* = 17.1 Hz, 1H), 2.30 (ABd, *J* = 17.1 Hz, 1H), 3.20 (s, 3H), 4.14–4.15 (m, 1H), 5.54–5.55 (m, 1H), 6.70 (d, *J* = 8.1 Hz, 1H), 6.74 (t, *J* = 8.0 Hz, 1H), 7.12 (t, *J* = 7.4 Hz, 1H), 7.39 (d, *J* = 7.3 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.8 (CH), 26.2 (CH_2), 27.7 (CH_3), 29.9 (CH_3), 32.6 (C), 37.5 (CH_3), 42.5 (CH_2), 50.9 (CH_2), 86.5 (CH), 110.7 (CH), 115.5 (C), 118.5 (CH), 127.4 (CH), 127.6 (C), 128.4 (CH), 141.7 (C), 168.8 (C), 196.3 (C) ppm. IR (KBr): 2953, 1606, 1495, 1381, 1331, 1204, 820, 776, 613 cm^{-1}; Anal Calcd for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.06; H, 7.32; N, 5.09. 7-Benzyl-3,3-dimethyl-2,3,4,6,7,12-hexahydro-1*H*-6,12-methanodibenzo[*d*,*g*][1,3]oxazocin-1-one (**3c**); mp: 155–157 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.04 (s, 3H), 1.12 (s, 3H), 2.08–2.13 (m, 2H), 2.22 (ABd, *J* = 16.3 Hz, 1H), 2.26 (ABd, *J* = 16.3 Hz, 1H), 2.28 (ABd, *J* = 16.1 Hz, 1H), 2.32 (ABd, *J* = 16.1 Hz, 1H), 4.22–4.23 (m, 1H), 4.74 (ABd, *J* = 17.4 Hz, 1H), 4.94 (ABd, *J* = 17.4 Hz, 1H), 5.64–5.65 (m, 1H), 6.60 (d, *J* = 8.1 Hz, 1H), 6.76 (t, *J* = 6.9 Hz, 1H), 7.02 (t, *J* = 7.4 Hz, 1H), 7.26–7.33 (m, 3H), 7.38 (t, *J* = 7.3 Hz, 2H), 7.47 (d, *J* = 7.3 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 26.0 (CH), 26.4 (CH_2), 27.9 (CH_3), 29.9 (CH_3), 32.6 (C), 42.5 (CH_2), 51.0 (CH_2), 53.5 (CH_2), 85.3 (CH), 111.3 (CH), 115.4 (C), 118.7 (CH), 126.7 (CH), 127.51 (CH), 127.54 (CH), 127.55 (C), 128.6 (CH), 129.2 (CH), 138.6 (C), 141.1 (C), 168.4 (C), 196.4 (C) ppm. IR (KBr): 2947, 1652, 1618, 1495, 1447, 1382, 983, 786, 751 cm^{-1}; Anal Calcd for $C_{24}H_{25}NO_2$: C, 80.19; H, 7.01; N, 3.90. Found: C, 80.34; H, 6.88; N, 4.01. 7-Allyl-3,3-dimethyl-2,3,4,6,7,12-hexahydro-1*H*-6,12-methanodibenzo[*d*,*g*][1,3]oxazocin-1-one (**3e**); mp: 102–104 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.99 (s, 3H), 1.09 (s, 3H), 1.97 (ddd, *J* = 12.7, 2.4, 2.3 Hz, 1H), 2.04 (ddd, *J* = 12.7, 3.1, 3.0 Hz, 1H), 2.18 (ABd, *J* = 16.3 Hz, 1H), 2.21 (ABd, *J* = 16.3 Hz, 1H), 2.24 (ABd, *J* = 17.3 Hz, 1H), 2.29 (ABd, *J* = 17.3 Hz, 1H), 4.06–4.10 (m, 1H), 4.14–4.15 (m, 1H), 4.26–4.31 (m, 1H), 5.17–5.22 (m, 2H), 5.54–5.55 (m, 1H), 5.88–5.95 (m, 1H), 6.66 (d, *J* = 8.1 Hz, 1H), 6.73 (t, *J* = 7.3 Hz, 1H), 7.08 (t, *J* = 7.4 Hz, 1H), 7.41 (d, *J* = 7.3 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.9 (CH), 26.3 (CH_2), 27.7 (CH_3), 29.9 (CH_3), 32.6 (C), 42.5 (CH_2), 50.9 (CH_2), 52.1 (CH_2), 84.9 (CH), 111.2 (CH), 115.3 (C), 116.6 (CH_2), 118.5 (CH), 127.4 (CH), 127.6 (C), 128.5 (CH), 133.9 (CH), 140.7 (C), 168.6 (C), 196.6 (C) ppm. IR

(KBr): 2961, 1618, 1496, 1384, 1044, 750 cm^{-1}; Anal Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.44; H, 7.55; N, 4.60. 3,3,6,7-Tetramethyl-2,3,4,6,7,12-hexahydro-1*H*-6,12-methanodibenzo[*d*,*g*][1,3] oxazocin-1-one (**3h**); mp: 126–128 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.98 (s, 3H), 1.08 (s, 3H), 1.82 (s, 3H), 1.98 (dd, *J* = 12.9, 3.4 Hz, 1H), 2.05 (dd, *J* = 12.9, 2.5 Hz, 1H), 2.18 (s, 2H), 2.25 (s, 2H), 3.08 (s, 3H), 4.05–4.06 (m, 1H), 6.68 (d, *J* = 8.1 Hz, 1H), 6.71 (t, *J* = 8.0 Hz, 1H), 7.10 (t, *J* = 7.4 Hz, 1H), 7.36 (d, *J* = 7.3 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 26.1 (CH_3), 27.68 (CH_3), 27.74 (CH), 29.9 (CH_3), 32.2 (CH_3), 32.6 (C), 34.9 (CH_2), 42.6 (CH_2), 51.0 (CH_2), 88.6 (C), 111.5 (CH), 114.4 (C), 118.2 (CH), 127.3 (CH), 127.9 (CH), 128.5 (C), 143.5 (C), 168.9 (C), 196.7 (C) ppm. IR (KBr): 2953, 1606, 1495, 1381, 1331, 1204, 820, 776, 613 cm^{-1}; Anal Calcd for $C_{19}H_{23}NO_2$: C, 76.73; H, 7.80; N, 4.71. Found: C, 76.51; H, 7.94; N, 4.62. 1-(1-Methyl-4-methyl-1,6-dihydro-2*H*-2,6-methano-3,1-benzoxazocin-5-yl)ethanone (**3i**); mp: 111–113 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.93 (ddd, *J* = 12.6, 2.6, 2.4 Hz, 1H), 1.99 (ddd, *J* = 12.6, 3.1, 3.0 Hz, 1H), 2.25 (s, 3H), 2.37 (s, 3H), 3.19 (s, 3H), 4.19–4.20 (m, 1H), 5.42–5.43 (m, 1H), 6.71 (d, *J* = 8.3 Hz, 1H), 6.74 (t, *J* = 7.4 Hz, 1H), 7.15 (t, *J* = 7.4 Hz, 1H), 7.31 (d, *J* = 7.3 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.8 (CH_3), 25.9 (CH_2), 29.3 (CH), 31.5 (CH_3), 37.4 (CH_3), 85.0 (CH), 110.8 (CH), 118.0 (C), 118.1 (CH), 127.6 (CH), 127.7 (C), 127.8 (CH), 142.0 (C), 163.8 (C), 197.5 (C) ppm. IR (KBr): 2947, 1652, 1618, 1495, 1447, 1382, 983, 786, 751 cm^{-1}; Anal Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.88; H, 7.15; N, 5.66.