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Multi-purpose functionality for the structural elaboration of the piperazine-2,5-dione motif

Christina L. L. Chai,* John A. Elix and Paul B. Huleatt

Department of Chemistry, The Faculties, Australian National University, Canberra, ACT 0200, Australia

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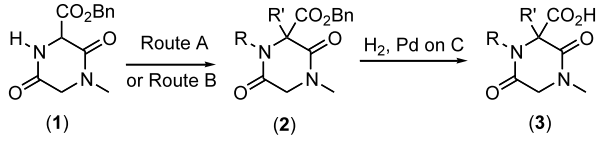
Abstract—Mild methods for controlled *C*- and *N*-alkylation of 3-benzyloxycarbonylpiperazine-2,5-diones are reported. The benzyloxylcarbonyl substituent can also serve as latent functionality for *N*-acyliminium ion formation and subsequent trapping enables installation of new carbon and/or heteroatom substituents.

The piperazine-2,5-dione motif is found in a number of biologically active natural products.[1] The structural complexities of these natural products range from simple derivatives of piperazine-2,5-diones, e.g. phenylahistin[2] to highly complex functionalized derivatives e.g. scabrosin esters.[3] In recent years, our studies have identified the need to develop rapid and efficient routes for the selective functionalization of piperazinediones. The successful application of existing methodologies for α-carbon functionalization via the corresponding bromides is highly dependent on the systems to be synthesized due to the influence of steric and electronic factors.[4] Other methods for α-carbon functionalization, e.g. alkylation, rely on the generation of the α-anion and this frequently requires the use of strong bases and harsh reaction conditions.[5] Mindful of these problems, we sought to develop an alternative multi-directional approach to the α-functionalisation of the piperazine-2,5-dione ring.

Our plan involved the use of an alkoxycarbonyl group as a temporary multi-purpose appendage on the piperazine-2,5-dione ring. Specifically, the alkoxycarbonyl group will serve (i) to enhance reactivity of the α-carbon center (ii) to direct regioselectivity and (iii) to enable the installation of carbon and/or heteroatom substituents where desired.

Thus, benzyloxycarbonylpiperazine-2,5-dione **1** was readily synthesized following modifications of literature procedures.[6] Dibenzyl aminomalonate was coupled with Boc-sarcosine under standard peptide coupling procedures (DCC/HOBt). The Boc group of the dipeptide was then cleaved using trifluoroacetic acid and following a basic workup procedure, cyclization of the dipeptide was induced thermally to give the piperazine-2,5-dione **1**. With this key piperazinedione in hand, chemoselective *N*- or *C*-alkylation can be effected depending on the alkylating conditions employed (Scheme 1, Table 1).[†] For example, selective *N*-methyl-



Scheme 1. *Reagents and conditions*: Route A: For R = Me (i) K_2CO_3, Me_2SO_4 (ii) K_2CO_3 or NaH, R′X; Route B: (i) K_2CO_3, R′X (ii) NaH, RX.

Table 1.

Compound	R	R′	Yields (%)
2a	Me	H	89
2b	H	Me	Quantitative
2c	H	Et	90
2d	H	Bn	Quantitative
2e	H	Allyl	82
2f	Me	Me	88
2g	Me	Bn	85
2h	Ac	H	91

Keywords: *N*-acyliminium ions; alkylations; amino acids and derivatives; trapping reactions.

* Corresponding author. Fax: +61-2-6125 0760; e-mail: christina.chai@anu.edu.au

[†] All new compounds gave satisfactory spectroscopic and analytical data.

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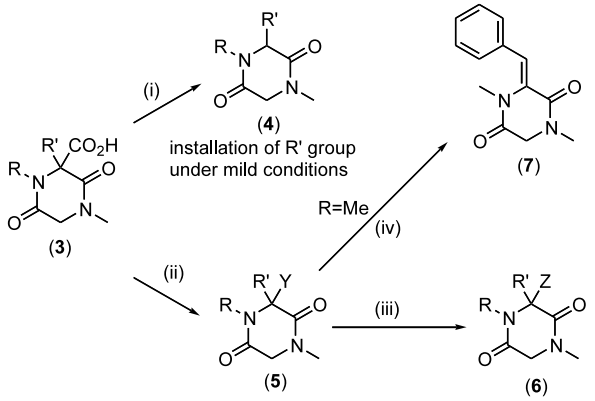
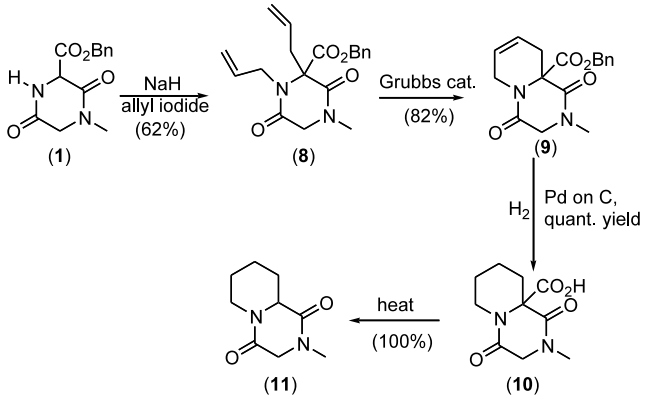


Scheme 2. *Reagents and conditions*: (i) heat; (ii) for Y = OAc, DIB, I_2; for Y = OMe, DIB, I_2 followed by MeOH; (iii) For Z = SAc, AcSH; for Z = allyl, 1.1 equiv. $BF_3{\cdot}OEt_2$, 5 equiv. allylTMS; (iv) 1.1 equiv. $BF_3{\cdot}OEt_2$.

Table 2.

Compound	R	R′	Y	Z	Yields (%)
5a	Me	H	OMe	–	76
5b	Me	H	OAc	–	83
5c	Me	Me	OMe	–	77
5d	Me	Me	OAc	–	55
5e	Me	Bn	OAc	–	74
6a	Me	H	–	SAc	74
6b	Me	H	–	Allyl	68
6c	Me	Me	–	SAc	80
6d	Me	Me	–	Allyl	66



Scheme 3.

ation of **1** to give piperazinedione **2** (R = Me, R′ = H) can be achieved using potassium carbonate and dimethyl sulfate. In contrast when piperazinedione **1** was treated with potassium carbonate and a variety of alkyl halides, the *C*-alkylated piperazinediones of type **2** (R′ = alkyl, R = H) were obtained in excellent yields. The monoalkylated piperazinediones of type **2** can be subsequently *C*- or *N*-alkylated. Alternatively, *N*-acetyl-3-benzyloxycarbonylpiperazine-2,5-dione (**2**, R = Ac, R′ = H) can be synthesized from 3-benzyloxycarbonylpiperazine-2,5-dione **1** using acetic anhydride, in the presence of DMAP.

Thus, in this manner, the benzyloxycarbonyl substituent activates the adjacent α-carbon position of the piperazine-2,5-dione to alkylation and negates the use of strong bases in proton abstraction. Efficient removal of the benzyloxycarbonyl substituent via hydrogenolysis then furnishes the corresponding 3-carboxypiperazine-2,5-dione **3**. It should be noted that an ethoxycarbonyl equivalent of **1** can be utilized in a similar manner. In this case, saponification of the ethyl ester gives access to the 3-carboxypiperazine-2,5-dione **3**. With the 3-carboxypiperazine-2,5-dione **3** in hand, thermal decarboxylation gives rise to the α-alkylated piperazine-2,5-diones **4**. This constitutes an overall synthesis of *N*- and α-dialkylated piperazine-2,5-diones **4** from 3-benzyloxycarbonylpiperazine-2,5-dione **1**.

The carboxy group of piperazine-2,5-dione **3** can also serve as a masked functionality to other carbon and/or heteroatom substituents. When carboxypiperazinediones of type **3** were treated with diacetoxyiodobenzene (DIB)/I_2, acetoxy derivatives (**5**, Y = OAc) were formed. Correspondingly reactions of piperazinedione **3** with DIB/I_2 followed by addition of methanol led to formation of the methoxy derivatives (**5**, Y = OMe) (Scheme 2, Table 2). The formation of these oxygenated derivatives under the reaction conditions above presumably occurs via a DIB promoted radical decarboxylation[7] to give the intermediate α-carbon centered radical of the piperazinedione. In the presence of DIB, the radical is oxidized to the *N*-acyliminium ion which is then trapped by nucleophiles present in the reaction mixture.

The oxygenated piperazine-2,5-dione derivatives **5** (Y = OAc, OMe) can be readily converted to the *N*-acyliminium ion. In trapping this highly reactive species with a variety of nucleophiles the synthetic potential of these systems is realized.[8] For example, treatment of **5a** (R = Me, R′ = H, Y = OMe) with $BF_3{\cdot}OEt_2$, in the presence allyltrimethylsilane gave the corresponding allyl compound **6b** in 68% yield, Table 2. Alternatively, in the absence of a nucleophile the *N*-acyliminium ion undergoes rearrangement to the ylidenepiperazine-2,5-dione. Treatment of **5e** (R = Me, R′ = Bn, Y = OAc) with $BF_3{\cdot}OEt_2$ in dichloromethane gave the 3-benzylidenepiperazine-2,5-dione **7** as a single diastereomer in 76% yield (Scheme 2). The spectroscopic data obtained for piperazine-2,5-dione **7** was consistent with the *Z*-isomer previously reported in the literature.[9]

In this manner, directed mono and dual functionalization of piperazinediones can be achieved and the scope of these reactions is summarized in Scheme 2. It should be noted that the approach reported here leads to compounds that cannot be readily synthesized using previously reported literature procedures. Hence our methods are orthogonal to and nicely complement existing methodologies.

To illustrate the versatility of alkoxycarbonylpiperazine-2,5-diones **1** in synthesis, conformationally constrained α-amino acid derivatives of pipecolic acid and baikiain are targeted (Scheme 3). Thus, piperazine-2,5-

dione **1** was converted to the diallylated piperazinedione **8** using sodium hydride and allyl iodide. Ring-closing metathesis of the diallylated piperazinedione **8** using the first generation Grubb's catalyst gave the cyclic alkene **9** in 82% yield. When the alkene was reacted with hydrogen in the presence of 10% Pd on C, the saturated carboxylic acid **10** was obtained in quantitative yield. With this compound in hand, the known[10] pipecolic acid derivative **11** was accessed via thermal decarboxylation of **10**.

Further work describing the applications of this strategy to the synthesis of piperazinedione-containing natural products as well as to optically pure non-proteinogenic amino acids will be reported in due course.

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