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Methylene Piperazine-2,5-diones as Templates for the Synthesis of Amino Acid Derivatives

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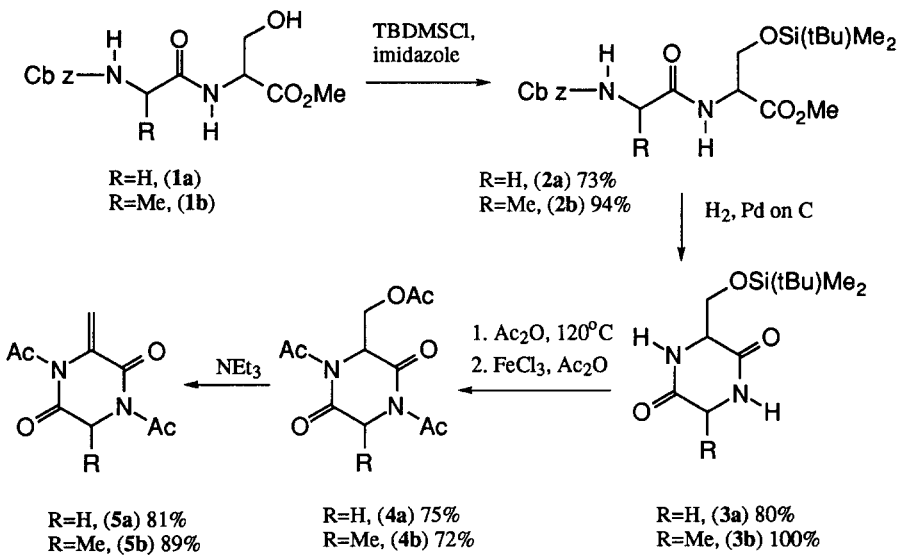
Abstract: Methylene piperazine-2,5-diones **5a** and **5b** are important synthetic intermediates. The preparation as well as the use of these compounds in the synthesis of amino acid derivatives are described. Our studies demonstrate that excellent chiral induction in carbon-carbon bond forming reactions can be obtained with methylene piperazinedione **5b**.

Due to the biological importance of chiral proteinogenic and non-proteinogenic amino acids, much effort has been invested in the development of methods for the synthesis of such compounds.[1,2] In particular, chiral auxiliaries forming part of cyclic templates derived from amino acids have been successfully utilised in the asymmetric synthesis of amino acids.[3-8] For example, Schöllkopf successfully synthesised optically active amino acids *via* bis- lactim ethers of piperazine-2,5-diones[6,7] and in a recent study by Easton et al,[8] α-halopiperazine-2,5-diones were used in the asymmetric synthesis of amino acid derivatives. However, very little has been reported on the use of unsaturated piperazine-2,5-diones as synthetic intermediates in asymmetric synthesis.[9,10] In this paper, we report the first use of methylene piperazine-2,5-diones in radical carbon-carbon bond forming reactions and demonstrate that these systems clearly have enormous potential in the synthesis of chiral and achiral amino acid derivatives.

The methylene piperazine-2,5-diones **5a** and **5b** were synthesised from Cbz-glycyl-(*L*)-serine methyl ester (**1a**) and Cbz-(*L*)-alanyl-(*L*)-serine methyl ester (**1b**) following the scheme outlined (Scheme 1).[11] The Cbz-dipeptide esters were converted to the corresponding TBDMS ethers (**2a**,**2b**) followed by hydrogenolysis (10% Pd/C in MeOH) to give piperazinediones **3a** and **3b** in 80% and quantitative yields respectively. *N*,*N'*-diacetylation of the piperazinediones **3a** and **3b**, followed by treatment of the crude reaction mixture with ferric chloride in acetic anhydride gave the acetoxy derivatives (**4a**) and (**4b**) in overall isolated yields of 75% and 72% respectively.[12] Treatment of the corresponding acetoxy piperazinediones with triethylamine gave the desired methylene piperazinediones **5a** and **5b** in excellent yields.[13]

The addition of alkyl radicals to methylene piperazine-2,5-diones was examined using the mercury method.[14,15] Here alkyl radicals (isopropyl and cyclohexyl) were generated (from the reaction of RHgCl and $NaBH_4$) in the presence of the methylene piperazinediones.[16] The experimental results are summarised in Table 1.

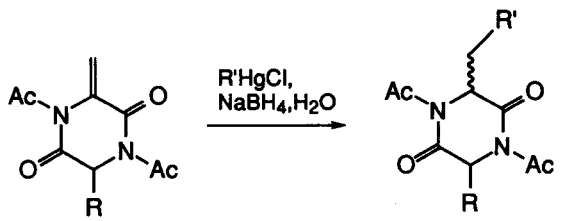


Scheme 1.

The results show that addition of alkyl radicals to the methylene piperazinedione **5a** gave the desired addition adduct in reasonable yields. The adducts **6a** and **7a** are easily identified by ^{1}H n.m.r. spectroscopy as the ring methylene hydrogens are characterised by doublets at 4.1 and 5.1 ppm.[17] This is clearly different to the singlet observed at 4.56 ppm for the same hydrogens in the unsaturated piperazine-2,5-dione **5a**.

The addition of alkyl radicals to piperazinedione **5b** gave addition adducts in yields similar to that above. However, using a combination of ^{1}H n.m.r., ^{13}C n.m.r. spectroscopy and GC/MS techniques, only one diastereomer was observed.[18] The stereochemistry of the diastereomer resulting from the addition of isopropyl radical to **5b** was ascertained to be *cis* by comparison of data with authentic 1,4-diacetyl-6-methyl-3-(2-methylpropyl)piperazine-2,5-dione, synthesised from Cbz-(*L*)-Leu-(*L*)-Ala methyl ester. The stereochemistry of the addition adduct **7b** was not determined separately but was assumed to be *cis* by analogy to the results above.

The studies above show that high diastereofacial selection is observed in the addition of alkyl radicals to methylene piperazinedione **5b**. The sole diastereomer must result from the preferential quenching of the addition adduct radical by the hydrogen donor (R'HgH) at the opposite face to the substituent (R=Me) at the remote α-carbon position. The radical centre is most likely to be planar and it is apparent that the methyl substituent shields one face of the molecule. Excellent diastereoselectivity is obtained despite the relatively small steric bulk of the methyl substituent. The effective bulk of the methyl substituent may be enhanced due to conformational preferences. For example, conformational studies of piperazinediones where *N*-substituents are present have shown the preference for α-carbon substituents to reside in pseudoaxial positions.[19,20]



R=H, (**5a**)
R=Me, (**5b**)

R=H, (**6a**,**7a**)
R=Me, (**6b**,**7b**)

Table1. Radical Addition to Methylene Piperazinediones **5a** and **5b**

Piperazinedione	Products	Diastereoselectivity	Isolated yields
R=H, (**5a**)	R'=isopropyl, (**6a**) R'=cyclohexyl, (**7a**)	- -	48% 46%
R=Me, (**5b**)	R'=isopropyl, (**6b**) R'=cyclohexyl, (**7b**)	*cis*-isomer only one isomer only	46% 49%

The results above strongly demonstrate that methylene piperazinediones have considerable potential as templates for the synthesis of amino acid derivatives, where radical addition reactions are used in the synthesis of new carbon-carbon bonds. The scope of these reactions utilising alkylmercury halides is limited only by the availability of these compounds. Alkylmercury halides are excellent sources of alkyl radicals and hence there is the potential to add a wide range of groups using this method.[14,15] In addition, the use of methylene piperazinediones as radical traps need not be limited to the mercury method. Other methods for radical addition exist[21] and these are currently under investigation. The high asymmetric induction observed for reactions with methylene piperazinedione **5b** is encouraging and current attempts are directed at elucidating factors which control the diastereoselectivities of radical addition. Such information will be relevant in the design of templates for asymmetric synthesis.

Acknowledgments

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11. New compounds gave satisfactory spectral, analytical and/or high resolution mass spectral data in accordance with the assigned structures.
12. **4a**: ^{1}H n.m.r. δ 2.05 (s, 3H, OAc); 2.58 (s, 3H, NAc); 2.59 (s, 3H, NAc); 4.19 (d, *J*=18 Hz, 1H, ring CH_AH_B); 4.46 (dd, *J*=3, 12 Hz, 2H, CH_AH_BOAc); 4.56 (dd, *J*=3, 12 Hz, 2H, CH_AH_BOAc); 4.98 (d, *J*=18 Hz, 1H, ring CH_AH_B); 5.35 (m, 1H, $CHCH_2$). **4b**: ^{1}H n.m.r. (*L,L*)-isomer δ 1.7 (d, *J*=7 Hz, 3H, $CHCH_3$); 2.06 (s, 3H, OAc); 2.55 (s, 3H, NAc); 2.56 (s, 3H, NAc); 4.45 (dd, *J*=3, 12 Hz, 1H, CH_AH_BOAc); 4.54 (dd, *J*=3, 12 Hz, 1H, CH_AH_BOAc); 5.19 (q, 1H, $CHCH_3$); 5.34 (m, 1H, $CHCH_2O$).
13. **5a**: ^{1}H n.m.r. δ 2.59 (s, 3H, NAc); 2.63 (s, 3H, NAc); 4.56 (s, 2H, ring CH_2); 6.09 (d, *J*= 1 Hz, 1H, $C=CH_AH_B$); 6.52 (d, *J*= 1 Hz, 1H, $C=CH_AH_B$). **5b**: ^{1}H n.m.r. δ 1.54 (d, *J*=7 Hz, 3H, $CHCH_3$); 2.58 (s, 3H, NAc); 2.63 (s, 3H, NAc); 5.29 (q, *J*=7 Hz, 1H, $CHCH_3$); 6.10 (d, *J*=1 Hz, 1H, $C=CH_AH_B$); 6.53 (d, *J*=1 Hz, $C=CH_AH_B$).
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16. To a vigorously stirred solution of methylene piperazinedione in dichloromethane (c. 0.35 M) was added alkylmercury chloride (2.4 mole equivalents). This was followed by the dropwise addition of a solution $NaBH_4$ (10 mole equivalents) in H_2O (0.4 M).
17. **6a**: ^{1}H n.m.r. δ 0.98 (d, *J*=6 Hz, 3H, $CH(CH_3)_2$); 1.05 (d, *J*=6 Hz, 3H, $CH(CH_3)_2$); 1.55 (m, 1H, $CH(CH_3)_2$); 1.85 (m, 2H, $CHCH_2CH(CH_3)_2$); 2.56 (s, 3H, CHNAc); 2.62 (s, 3H, CH_2NAc); 4.06 (d, 1H, *J*=18 Hz ring CH_AH_B); 5.12 (d, *J*=18 Hz, 1H, ring CH_AH_B); 5.30 (m, 1H, $CHCH_2CH(CH_3)_2$). **7a**: ^{1}H n.m.r. δ 0.98 -1.78 (m, 11H, cyclohexyl and m, 2H, $CH_2C_6H_{11}$); 2.56 (s, 3H, CH_2NAc); 2.59 (s, 3H, CHNAc); 4.10 (dd, *J*=18 Hz, 1H, ring CH_AH_B); 5.15 (d, *J*=18 Hz, 1H, ring CH_AH_B), 5.32 (m, 1H, $CHCH_2C_6H_{11}$) .
18. **6b**: ^{1}H n.m.r. δ 0.99 (d, *J*=6 Hz, 3H, $(CH_3)_2CH$); 1.06 (d, *J*=6 Hz, 3H, $(CH_3)_2CH$); 1.64 (d, *J*=7 Hz, 3H, $CHCH_3$); 1.8 (m, 3H, CH_2CHMe_2 and CH_2CHMe_2); 2.54 (s, 3H, NAc); 2.57 (s, 3H, NAc); 5.19 (q, 1H, $CHCH_3$); 5.25 (m, 1H, $CHCH_2CHMe_2$). **7b**: ^{1}H n.m.r. δ 0.80-2.0 (m, 11H, cyclohexyl and m, 2H, $CH_2C_6H_{11}$); 1.65 (d, *J*=7 Hz, 3H, $CHCH_3$); 2.49 (s, 3H, NAc); 2.58 (s, 3H, NAc); 5.19 (q, 1H, $CHCH_3$); 5.29 (m, 1H, $CHCH_2C_6H_{11}$).
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