

# Kinetic resolution of amines by acylation using 3-diacylaminoquinazolin-4(3*H*)-ones

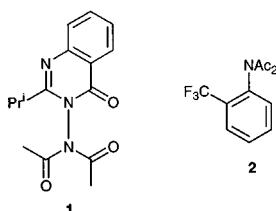
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Four diastereoisomeric 3-diacylaminoquinazolinones **8a–d** have been separated and identified by X-ray structure determinations on three of them: their stoichiometric reactions with  $\alpha$ -phenylethylamine and with 2-methylpiperidine (2 equiv. of amine) gave the corresponding *N*-(2-acetoxypropanoyl)amine and unreacted amine in high diastereomeric/enantiomeric excess.

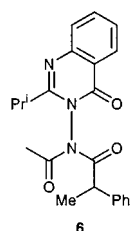
3-Diacylaminoquinazolinones (DAQs), *e.g.* **1**, are highly selective acylating agents for primary amines in the presence of secondary amines and for the less hindered of two secondary amines.<sup>1</sup> Recently the *N,N*-diacetamide **2** has been claimed to be even more chemoselective than DAQ **1** as an acetylating agent: a 1:1 mixture of pyrrolidine and piperidine ( $\Delta pK_a = 0.01$ ) reacts with **2** to give a 15:1 ratio of the corresponding *N*-acetylated amines.<sup>2</sup>



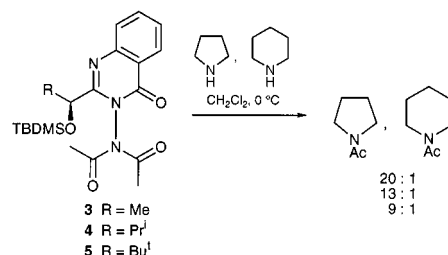
The DAQs **3**, **4** and **5** were available to us by acetylation of the corresponding 3-aminoquinazolinones<sup>3</sup> and, when reacted with a mixture of pyrrolidine and piperidine (1 equiv. each) at 0 °C in CH<sub>2</sub>Cl<sub>2</sub> gave the ratios of the corresponding amides shown in Scheme 1. Unexpectedly, the chemoselectivity increases as the substituent R on the chiral centre decreases in size from Bu<sup>t</sup> → Me with a 20:1 ratio for methyl.<sup>†</sup>

Since DAQs **3**, **4** and **5** are enantiopure we were particularly interested in a greater potential advantage which their use offered over that of *e.g.* **2**, namely as enantioselective acylating agents.<sup>4</sup> However, reaction of DAQ **3** (1 equiv.) with racemic 2-methylpiperidine (2 equiv.) gave a sample of recovered amine having zero optical rotation and hence there is no kinetic resolution in this acylation.

For 3-aminoquinazolinones *N,N*-disubstituted with different acyl groups, we have previously shown that the *N–N* bond is a chiral axis: in DAQ **6** the presence of two chiral elements gives rise to diastereoisomers with a barrier  $\Delta G^\ddagger = 121 \text{ kJ mol}^{-1}$  for their interconversion by rotation around the *N–N* bond.<sup>4</sup>



Successive acylation of enantiopure 3-aminoquinazolinone **7**<sup>3</sup> with (*S*)-2-acetoxypropanoyl chloride and isobutanoyl chlo-



Scheme 1

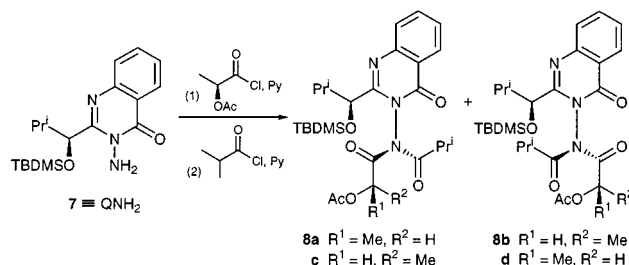
ride (Scheme 2) gave four DAQ diastereoisomers **8a–d** in order of their elution on chromatography (see below). The major diastereoisomer **8b** was separated by crystallisation (35%) after flash chromatography to remove unreacted mono-acylquinazolinone (MAQ) and pure samples of the other three, **8a** (5%), **8c** (7%) and **8d** (26%), were obtained by separation using a chromatotron.

X-Ray crystal structure determinations of DAQs **8b** and **8c** (Fig. 1) showed them to have the expected (*S*)-configuration at their  $\alpha$ -acetoxypropanoyl chiral centres but different configurations at their *N–N* chiral axes.<sup>‡</sup> Heating (CDCl<sub>3</sub>, 60 °C, 42 h) interconverted **8b** and **8c** and gave a 5:4 ratio respectively at equilibrium, presumably as a result of rotation around the *N–N* bond: no interconversion with **8a** or **8d** occurred.

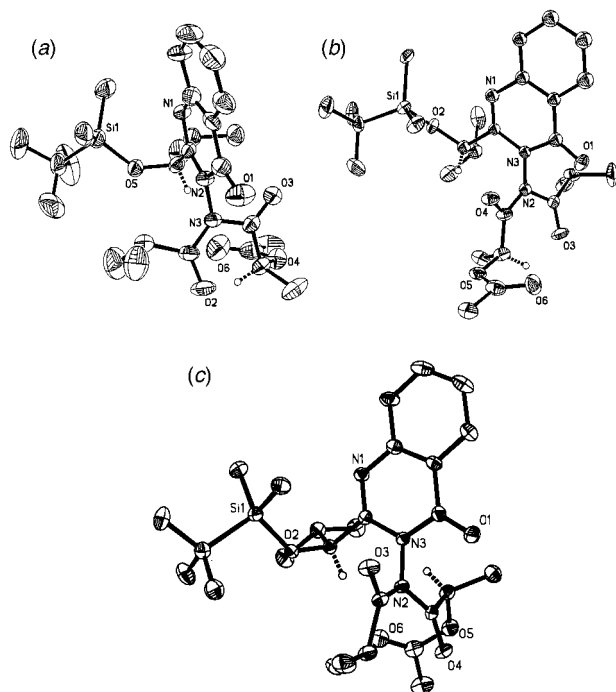
Diastereoisomers **8a** and **8d** arise from epimerisation at the  $\alpha$ -acetoxypropanoyl centre as shown by the (*R*)-configuration in the X-ray crystal structure of **8d** (Fig. 1).<sup>‡</sup> Interconversion of **8a** and **8d** by heating (CDCl<sub>3</sub>, 60 °C, 13 h) gave a 6:1 ratio at equilibrium, respectively: no interconversion with **8b** and **8c** occurred in this equilibrium.

Although in their crystal structures DAQ **8b–d** all have the usual<sup>4</sup> *exo/endo* conformation for their imides, **8b** and **8c** have their  $\alpha$ -acetoxypropanoyl groups *endo* and the isobutanoyl group *exo* whereas **8d** has the positions of these two groups reversed.

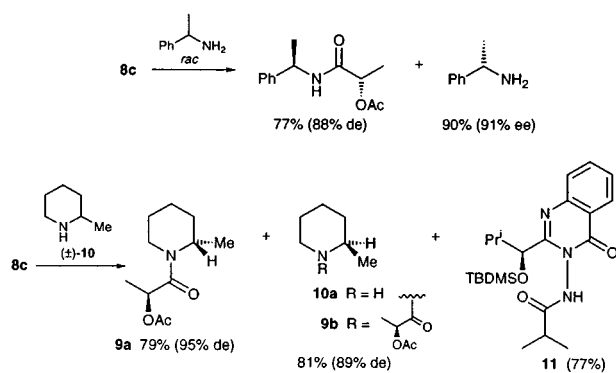
We find that these DAQs **8a–d** are enantioselective acylating agents for racemic amines. Thus DAQ **8c** (1 equiv.) reacts with  $\alpha$ -phenylethylamine (2 equiv.) in CH<sub>2</sub>Cl<sub>2</sub> at 5 °C to give (2*R*,2'*S*)-*N*-(2-acetoxypropanoyl)- $\alpha$ -phenylethylamine [77% based on (*R*)- $\alpha$ -phenylethylamine, 88% de] by NMR comparison with authentic samples of both diastereoisomers: the recovered *S* enantiomer of the amine [90% based on (*S*)- $\alpha$ -phenylethylamine] was of 91% ee from its specific rotation (Scheme 3).



Scheme 2



**Fig. 1** Molecular structures of (a) **8b**, (b) **8c** and (c) **8d** showing atom labelling schemes and 30% probability displacement parameters. H atoms at chiral centres are shown with dashed bonds, all other H atoms are omitted for clarity.



Reaction of DAQ **8c** (1 equiv.) with racemic 2-methylpiperidine **10** (2 equiv.) in  $\text{CH}_2\text{Cl}_2$  at  $5^\circ\text{C}$  for 24 h gave, after chromatography, monoacylquinazolinone (MAQ) **11** (77%) and (2*S*,2'*S*)-1-(2'-acetoxypropanoyl)-2-methylpiperidine **9a** (79%) (Scheme 3) whose diastereopurity (de) as measured by NMR spectroscopy was 95%. The unreacted 2-methylpiperidine enantiomer was recovered from the crude reaction mixture by extraction with HCl (2 M) and derivatised by reaction with (*S*)-2-acetoxypropanoyl chloride to give **9b** (81%) of 89% de: at 400 MHz and  $50^\circ\text{C}$  the  $\text{OCOCH}_3$  signals of diastereoisomers **9a** and **9b** are well separated. $\S$

Since DAQ **8b** was recovered unchanged when re-subjected to the conditions of the second acylation in Scheme 2, it appears that epimerisation at the 2-acetoxypropanoyl chiral centre

occurs in the second acylation step. $\P$  An alternative, more stereoselective route to these DAQs was to carry out the second acylation using the lithium salt of the MAQ. Thus reaction of the lithium salt of MAQ **11** with (*S*)-2-acetoxypropanoyl chloride gave DAQ **8c** (71%) and **8a** (8%) (based on recovered starting material), *i.e.* with less epimerisation than previously.

Kinetic resolution is usually carried out in the presence of excess of the substrate to maximise enantiopurity in its derivatised enantiomer. Even under the most testing conditions of stoichiometry as in Scheme 3, DAQ **8c** delivers both derivatised and unreacted enantiomers of the substrate with high enantioselectivity.

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## Notes and references

$\dagger$  This increase may be related to the preference for a defined conformation around the C–OSi bond in the (Q) 2-substituent in **3** but not in **4** or **5** (see R. S. Atkinson, M. P. Coogan and I. S. T. Lochrie, *Tetrahedron Lett.*, 1996, **37**, 5179).

$\ddagger$  *Crystal data* for **8b**:  $\text{C}_{27}\text{H}_{41}\text{N}_3\text{O}_6\text{Si}$ ,  $M = 531.72$ , orthorhombic, space group  $P2_12_12_1$ ,  $a = 10.146(1)$ ,  $b = 13.296(2)$ ,  $c = 22.618(3)$  Å,  $V = 3051.4(7)$  Å<sup>3</sup>,  $Z = 4$ ,  $\mu(\text{Mo-K}\alpha) = 0.118$  mm<sup>-1</sup>, 3845 reflections measured, 3639 unique ( $R_{\text{int}} = 0.013$ ) which were all used in calculations. Final  $R_1 = 0.052$  and  $wR_2 = 0.114$  (all data). For **8c**:  $\text{C}_{27}\text{H}_{41}\text{N}_3\text{O}_6\text{Si}$ ,  $M = 531.72$ , orthorhombic, space group  $P2_12_12_1$ ,  $a = 9.391(2)$ ,  $b = 13.554(6)$ ,  $c = 23.908(13)$  Å,  $V = 3043(2)$  Å<sup>3</sup>,  $Z = 4$ ,  $\mu(\text{Mo-K}\alpha) = 0.118$  mm<sup>-1</sup>, 3756 reflections measured, 3592 unique ( $R_{\text{int}} = 0.035$ ) which were all used in calculations. Final  $R_1 = 0.102$  and  $wR_2 = 0.309$  (all data). For **8d**:  $\text{C}_{27}\text{H}_{41}\text{N}_3\text{O}_6\text{Si}$ ,  $M = 531.72$ , orthorhombic, space group  $P2_12_12_1$ ,  $a = 12.152(9)$ ,  $b = 13.170(7)$ ,  $c = 18.293(9)$  Å,  $V = 2928(3)$  Å<sup>3</sup>,  $Z = 4$ ,  $\mu(\text{Mo-K}\alpha) = 0.118$  mm<sup>-1</sup>, 3666 reflections measured, 3455 unique ( $R_{\text{int}} = 0.155$ ) which were all used in calculations. Final  $R_1 = 0.044$  and  $wR_2 = 0.099$  (all data). Data were measured on a Siemens P4 diffractometer at 190 K using graphite monochromated Mo-K $\alpha$  radiation ( $\lambda = 0.7107$  Å) using an  $\omega$ -scan technique. Three standard reflections monitored every 100 scans showed no significant variation in intensity, the reflections were corrected for Lorentz and polarisation effects. The structures were solved by direct methods and refined by full-matrix least-squares on  $F^2$ . The absolute configurations of the compounds were established by the known configuration at the silyloxy substituted carbon atom. All examined crystals of **8c** diffracted weakly; to preserve an observed data to variable ratio of 6:1 the 13 most closely isotropic atoms were constrained to be isotropic. All hydrogen atoms were included in calculated positions (C–H = 0.96 Å) using a riding model. CCDC 182/1486. See <http://www.rsc.org/suppdata/cc/a9/a907970j/> for crystallographic data in .cif format.

$\S$  A mixture of amide diastereoisomers **9a** and **9b** was prepared by reaction of (*S*)-2-acetoxypropanoyl chloride with racemic 2-methylpiperidine. An authentic sample of amide **9b** was prepared from (*R*)-2-methylpiperidine,  $[\alpha]_{\text{D}}^{25}(\text{HCl salt}) 8.9$  ( $c$  2, EtOH), itself prepared from the racemic amine by resolution using (*R*)-mandelic acid.

$\P$  Significantly, the MAQ recovered from the reaction in Scheme 2 was also found to be a mixture of two diastereoisomers, epimeric at the 2-acetoxypropanoyl chiral centre.

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