N-Acetyl-*N*-acyl-3-aminoquinazolinones as chemoselective acetylating agents

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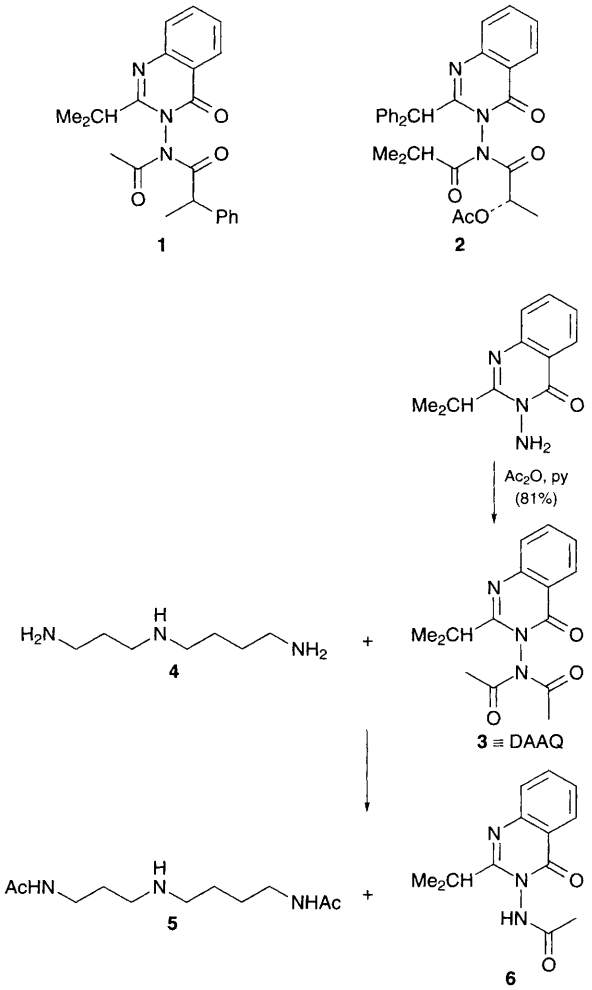
The title compounds, *e.g.* 3, are highly selective acetylating agents for primary amines in the presence of secondary amines and, in particular, for the less sterically hindered of two different secondary amines.

Rotation around the N–N bond in 3-diacylaminoquinazolinones is sufficiently retarded for this bond to constitute a chiral axis when two different acyl groups are present. Thus the two diastereoisomers of compound **1** have been separated and the barrier to their interconversion by rotation around the N–N bond has been measured (ΔG = 121 kJ mol^{-1}).[1]

These 3-diacylaminoquinazolinones are acylating agents for amines. We have shown that the two enantiopure diastereoisomers of compound **2** bring about the partial kinetic resolution of α-phenylethylamine, with the configuration of the N–N axis dominating the preferred sense of enantioselectivity and with exclusive reaction at the α-acetoxypropionyl carbonyl group.[1]

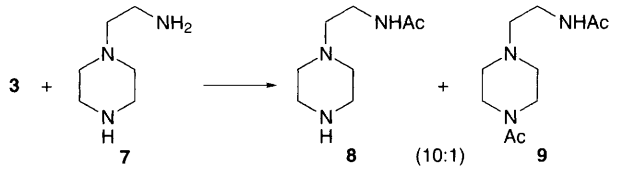
Acetylation of 3-amino-2-isopropylquinazolin-4(3*H*)-one with acetic anhydride–pyridine gives the *N*,*N*-diacetylaminoquinazolinone **3** (DAAQ) in 81% yield, mp 71.5–72 °C, Scheme 1.[2] Reaction of **3** (2 equiv.) with spermidine **4** gave the diamide **5** having only the terminal amino groups acetylated. This diamide **5** was freed from the byproduct 3-acetylaminoquinazolinone **6** by extraction into 0.1 mol dm^{-3} hydrochloric acid and isolated as its hydrochloride salt after freeze drying in 90% yield.



Scheme 1

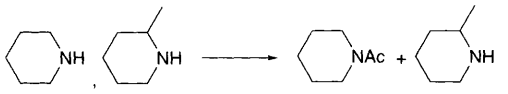
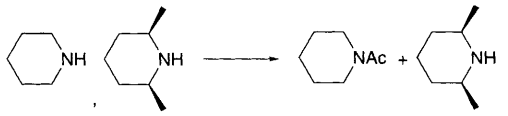
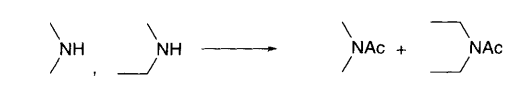
Reaction of **3** (1 equiv.) with *N*-(2-aminoethyl)piperazine **7** (1 equiv.) also resulted in selective acetylation of the primary amine giving amide **8**, Scheme 2: in this case, however, a minor amount of the *N*,*N*-diacetylated product **9** was also obtained (**8**:**9**, 10:1). Since no *N*,*N*,*N*-triacetylation product was detectable in the crude reaction product from spermidine **4** and DAAQ **3** above, the decreased selectivity in acetylation of compound **7** implied a greater reactivity of the six-membered (piperazine) ring amine over an acyclic dialkylamine towards acetylation by **3**. Accordingly, in the competitive reaction of piperidine (1 equiv.) and diethylamine (1 equiv.) with **3** (1 equiv.; see Table 1, entry 1), only signals from acetylpiperidine were discernible in the NMR spectrum of the crude reaction product by comparison with the NMR spectra of authentic acetylation products of both amines.

Competitive reactions of pairs of similar secondary amines with **3** were then examined and the results are given in Table 1. Comparison of the crude reaction product in each case was made with authentic samples of the possible amide products



Scheme 2

Table 1 Competitive reactions of amines with DAAQ **3**

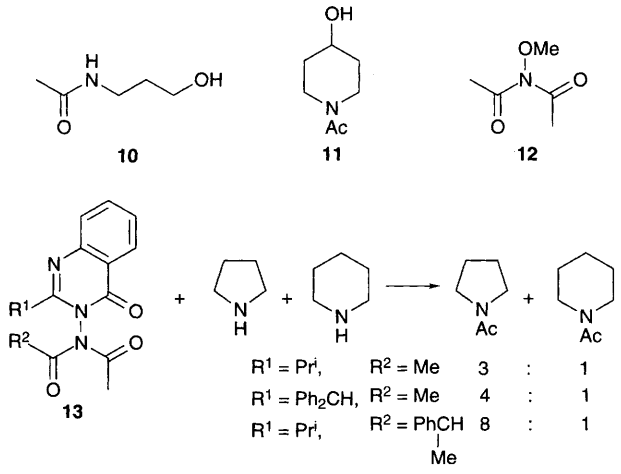
Entry	Amine[a]	Product
1		
2		
3[b]		
4		
5		

[a] The amines (1 equiv.) were treated with **3** (1 equiv.) in CH_2Cl_2 at room temp. for 10–30 min. [b] The mixture was heated under reflux for 6 h.

using NMR spectroscopy. Only in the competitive reaction of dimethylamine with *N*-ethylmethylamine (entry 5) were detectable amounts of both derivatives present (9 : 1, respectively).

Control experiments in which pairs of amines (Table 1) competed for acetic anhydride (1 equiv.) showed some selectivity, but nothing like comparable with that using **3**. Complete acetylation of diethylamine (1 equiv.) with **3** (1 equiv.) was found to require stirring in dichloromethane at room temperature for 2 d. No reaction between *cis*-2,6-dimethylpiperidine and **3** (1 : 1) was detected (*cf.* entry 3) even after heating under reflux in dichloromethane for 7 h: this amine was readily acetylated using acetic anhydride.

The acetylating agent **3** is less selective in competitive reactions with two primary amines, but does react preferentially



Scheme 3

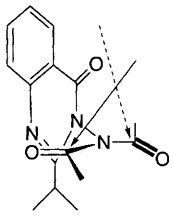


Fig. 1

with *sec*-butyl amine in the presence of *tert*-butylamine (> 10 : 1). Its reaction with alcohols does not occur under conditions required for the complete reaction of amines: 3-aminopropanol and 4-hydroxypiperidine give the corresponding *N*-acetylated derivatives **10** and **11**. These amides were easily separated from the *N*-acetylaminoquinazolinone by-product **6** by chromatography over silica.

We find that the *N*,*N*-diacetylmethoxyamine **12**, which has also been reported to bring about selective acetylation of the terminal amino groups of spermidine **4**,[3] is likewise a selective acetylating agent *e.g.* for piperidine in the presence of 2-methylpiperidine (*cf.* entry 2, Table 1). In fact both these acetylating agents **3** and **12** react with a mixture of pyrrolidine and piperidine to give a *ca.* 3 : 1 ratio of the corresponding amides.

As the results in Scheme 3 indicate, there is scope for increasing the selectivity of these *N*-acetyl-*N*-acylquinazolinones as acetylating agents by variation both of the quinazolinone 2-substituent and the unreactive *N*-acyl group.

The selectivity in these acetylations, based on our computer modelling studies, arises from attack by the amine on one face of one carbonyl group with the imide in the more stable *exo*–*endo*-conformation.[4] Thus in Fig. 1, the lower faces of both carbonyl groups are blocked by the 2-isopropyl substituent in **3**. Furthermore, assuming a tetrahedral attack on the carbonyl group by the amine, the trajectory shown as ---> is blocked by the quinazolinone carbonyl group leaving that indicated by → as the most likely.

We thank Mr Olivier Desmars and Miss Lucie Bednárová for experimental assistance in this work and the EPSRC for support (to E. B.). M. J. S. is a Royal Society University Research Fellow.

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Received, 7th February 1996; Com. 6/00920D