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3-(*N*,*N*-Diacylamino)quinazolin-4(3*H*)-ones as enantioselective acylating agents for amines

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Abstract

The presence of an N–N chiral axis in a 3-(*N*-benzoyl-*N*-isobutanoyl)aminoquinazolin-4(3*H*)-one (DAQ) bearing a chiral substituent in the 2-position of the quinazolinone allows separation of two enantiopure diastereoisomers; one of these diastereoisomers reacts with racemic 2-methylpiperidine to give (*R*)(+)-1-benzoyl-2-methylpiperidine (95% ee) and (*S*)-2-methylpiperidine (91% ee) even using stoichiometric quantities of reagents (1 equiv. DAQ: 2 equiv. amine).

We have shown previously that 3-diacylaminoquinazolin-4(3*H*)-ones (DAQs) containing a chiral centre in one of the acyl groups e.g. **1** are separable into diastereoisomers.[1] The additional chiral element in DAQ **1** is the N–N bond (a chiral axis) since two non-interconverting rotamers around this bond are present at room temperature: interconversion between the two diastereoisomers of DAQ **1** by rotation around the N–N bond takes place only on heating ($\Delta G^{\#}$=121 kJ mol^{-1}). We have also shown that 3-*N*,*N*-diacetylaminoquinazolinones e.g. **2** are highly selective acetylating agents for primary amines in the presence of secondary amines and for the less sterically hindered of two secondary amines.[2] For example, DAQ **2** reacts exclusively with piperidine in the presence of 2-methylpiperidine and with dimethylamine in the presence of diethylamine. This *chemoselectivity* in the reaction of DAQ **2** with the less hindered of two secondary amines we now find has a *stereoselective* counterpart — the preferential reaction of a diastereo- and enantio-pure DAQ with one enantiomer of a racemic secondary amine thus bringing about kinetic resolution of the amine.[3]

We prepared DAQ diastereoisomers **4a** and **4b** by sequential *N*-benzoylation and *N*-isobutanoylation of 3-aminoquinazolinone **3** which was itself prepared from (L)-valine in five steps without the need for chromatography (Scheme 1).[4] Separation of the DAQ diastereoisomers **4a** and **4b**, formed in a 1.6:1 ratio, was accomplished by Kieselgel chromatography[5] and an X-ray structure determination was carried out on the crystalline slower-eluted diastereoisomer **4b** (Fig. 1).[6]

In this crystal structure, the quinazolinone and imide planes,[7] linked by the N–N bond, are, as expected, approximately orthogonal but the conformations of the imide carbonyl groups are both *exo* and not

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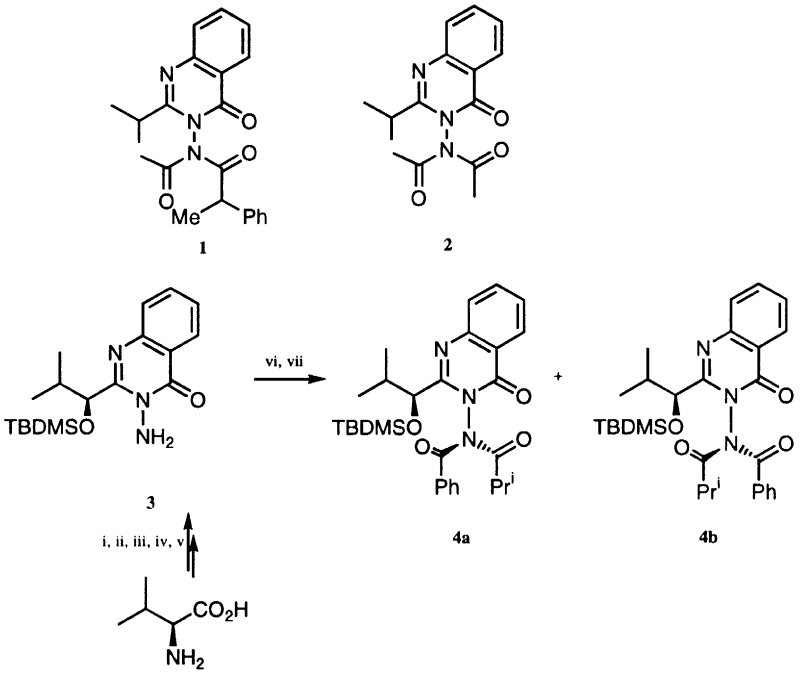


Scheme 1. Reagents: (i) $NaNO_2$, HOAc; (ii) $SOCl_2$; (iii) methyl anthranilate; (iv) NH_2NH_2, EtOH; (v) TBDMSCl, imidazole, DMF; (vi) PhCOCl, pyr.; (vii) Pr^iCOCl, pyr

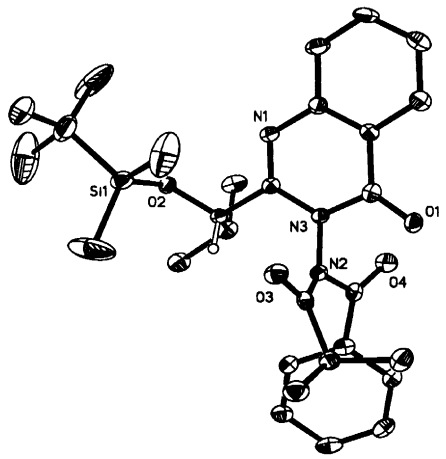


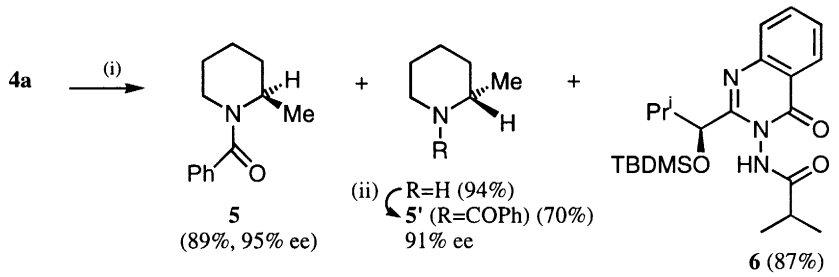
Fig. 1. Molecular structure of **4b**. Displacement parameters are shown at the 30% probability level, H atoms are omitted for clarity

exo–endo as has previously been found for other DAQs e.g. **1**.[1] As can be seen from Fig. 1, the benzoyl group has its benzene ring out of the plane of the carbonyl (dihedral angle 50.1° between the two planes). Moreover, the carbonyl group of the benzoyl is twisted out of the plane which would allow overlap of its π-bond with the *p*-orbital on the imide nitrogen.[8] The isobutanoyl group, by contrast, is oriented such that it can enjoy normal amide resonance with this imide nitrogen.

Both the non-amidic nature of the benzoyl carbonyl group and the absence of conjugation in the benzoyl unit presumably account for the completely chemoselective attack by amines, e.g. 2-methylpiperidine, on the benzoyl group of DAQ **4b**, i.e. the structures in the crystal and in solution

are probably similar. Likewise, DAQ **4a** (an oil) also undergoes attack by 2-methylpiperidine exclusively at the benzoyl group.[9]

Both DAQs **4a** and **4b** react enantioselectively with amines. Thus, reaction of DAQ **4a** (1 equiv.) with 2-methylpiperidine (2 equiv.) was carried out in dichloromethane at 5°C for 12 h. Unreacted 2-methylpiperidine was extracted with aqueous hydrochloric acid (2M) and the free amine converted to the *N*-benzoylamide **5′** (Scheme 2). The benzoylamide **5** formed in the reaction of **4a** with 2-methylpiperidine was isolated by flash chromatography of the crude reaction product obtained from the dichloromethane layer; the only other product isolated was the 3-isobutanoylaminoquinazolinone **6**. A summary of the yields, and calculated ees of products isolated from these reactions is given in Scheme 2.[10]



Scheme 2.

The ees in Scheme 2 were based on the optical rotation of a sample of (*S*)-1-benzoyl-2-methylpiperidine $[\alpha]_D$+32.9 (c=0.8, $CHCl_3$) prepared from (*S*)-2-methylpiperidine {$[\alpha]_D$ 8.9 (c=2, EtOH) lit.[11] 7.2 (c=6, EtOH)} itself obtained from the racemic amine by resolution using (*R*)-mandelic acid.[11] The enantiopurity of this (*S*)-2-methylpiperidine was independently confirmed by its derivatisation with (*S*)-2-acetoxypropanoyl chloride and by comparison of the NMR spectrum of the product with that of the mixture of diastereoisomers formed from racemic 2-methylpiperidine with the same acid chloride: at 400 MHz and 50°C the OCOCH_3 signals in the NMR spectrum of this mixture were completely separated.

A quantitative measure of the enantioselectivity of DAQ **4a** with 2-methylpiperidine was obtained by separation of enantiomers of this amine by classical resolution and by measuring the kinetics of the reactions of each of these enantiomers with DAQ **4a**. The relative rates of faster reacting:slower reacting amine enantiomers [k(*R*):k(*S*)] was calculated to be 27:1.

Reaction of DAQ **4b** (1 equiv.) with 2-methylpiperidine (2 equiv.) is slower and requires 3 days for complete reaction: significantly, it is the other enantiomer of 2-methylpiperidine which reacts giving *N*-benzoylamide **5′** (80% ee). Thus in these benzoylations with DAQs **4a** and **4b** it is the chiral axis which controls the sense of enantioselectivity.

Acknowledgements

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References

1. Atkinson, R. S.; Barker, E.; Edwards, P. J.; Thomson, G. A. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1047.
2. Atkinson, R. S.; Barker, E.; Sutcliffe, M. J. *Chem. Commun.* **1996**, 1051.

3. We have previously shown that partial kinetic resolution of α-phenylethylamine with a DAQ was possible (Ref. 1).
4. cf. Atkinson, R. S.; Ayscough, A. P.; Gattrell, W. T.; Raynham, T. M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2783.
5. Hunt, B. J.; Rigby, W. *Chem. and Ind.* **1967**, 1868.
6. Crystal data: **4a**, $C_{29}H_{39}N_3O_4Si$, M=521.72, orthorhombic, space group $P2_12_12_1$, a=9.061(1), b=15.181(2), c=21.423(12) Å, V=2947(2) Å^3, Z=4, D_c=1.176 g cm^{-3}, F(000)=1120, μ=0.116 mm^{-1}, crystal 0.72×0.37×0.22 mm, radiation Mo-Kα (λ=0.71069 Å), 160(2) K, 3253 data, 334 parameters, $R_1[F^2>2\sigma(F^2)]$=0.0537, wR_2=0.1354 (all data).
7. The imide nitrogen of DAQ **4a** is not exactly planar (Σ bond angle=353.3°).
8. For references to other twisted amides, see: Kondo, K.; Fujita, H.; Suzuki, T.; Murakami, Y. *Tetrahedron Lett.* **1999**, 40, 5577 and references cited therein.
9. By comparison, a competitive reaction of benzoyl chloride and isobutanoyl chloride for 2-methylpiperidine gave a 3:2 ratio of the corresponding amides, respectively.
10. The enantiopurity of the unreacted enantiomer was also determined by its reaction with (*S*)-α-acetoxylpropanoyl chloride: the de of the resulting amide was 89% as measured by NMR.
11. Craig, J.; Pindlar, A. R. *J. Org. Chem.* **1971**, 32, 3649.