Pergamon

Tetrahedron Letters 41 (2000) 2243–2246

TETRAHEDRON LETTERS

3-Di-[(*S*)-2-acetoxypropanoyl]aminoquinazolin-4(3*H*)-ones: stereostructure and application in kinetic resolution of amines

Abdullah G. Al-Sehemi, Robert S. Atkinson,* John Fawcett and David R. Russell

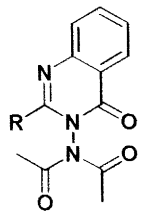
Department of Chemistry, Leicester University, Leicester, LE1 7RH, UK

Received 9 December 1999; accepted 18 January 2000

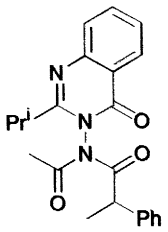
Abstract

Whereas 3-diacylaminoquinazolin-4(3*H*)-ones (DAQs) have been previously shown to undergo rapid *exo/endo–endo/exo* conformational interconversion of their imide carbonyl groups, the title DAQs are believed to exist in one single *exo/endo* form and consequently their N–N bonds are chiral axis: one of these DAQs, substituted with a diphenylmethyl group on the Q-2 position, reacts preferentially with one enantiomer of racemic 2-methyl-piperidine at the 2-acetoxypropanoyl imide carbonyl group (ee 94%).

3-Diacylaminoquinazolinones (DAQs) e.g. **1** are highly chemoselective acylating agents for primary amines over secondary amines and, in particular, for the less hindered of two secondary amines.[1] They are readily available by acylation of the corresponding 3-aminoquinazolinones; since the second acylation is slower than the first, DAQs bearing two different acyl groups are readily prepared.[2]



1 R = Pr^i
3 R = Et



2a/b

When the two acyl groups on the exocyclic nitrogen are different, the N–N bond is a chiral axis since the quinazolinone and imide-containing planes are orthogonal and no complete rotation around the N–N bond occurs at room temperature. The presence of a chiral centre in a substituent on the 2-position of the quinazolinone, or in one of the acyl groups, gives rise to diastereoisomeric DAQs e.g.

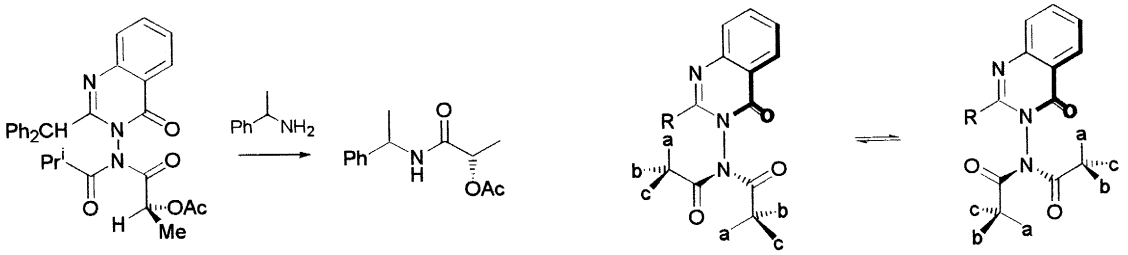
* Corresponding author.

0040-4039/00/$ - see front matter
PII: S0040-4039(00)00139-8

2a/**2b**: interconversion between these separated diastereoisomers (atropisomers) takes place on heating in toluene at 100°C over 1 h ($\Delta G^{\#}$ 121 kJ mol^{-1}) by rotation around the N–N bond.[2]

Evidence for the *exo/endo* conformation for the imide moiety in DAQ **1** follows from the NMR spectrum of DAQ **3**. At room temperature, the acetyl methyl signals are present as a broadened singlet: at −85°C in $^{2}H_{6}$-acetone this singlet has separated into two singlets of equal intensity. At this low temperature also, the methylene protons of the ethyl group become diastereotopic because the N–N bond is now a chiral axis. The *exo/endo* conformation is also that adopted in crystal structures of these DAQs.[2]

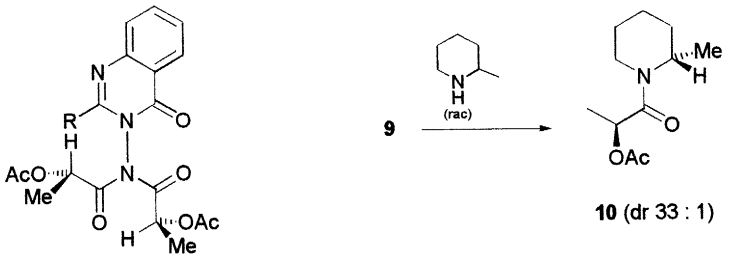
The chemoselectivity shown by achiral DAQ **1** referred to above has a stereoselective counterpart when the chiral DAQ is used in enantiopure form. Thus DAQ **4** prepared by successive acylation of the 3-aminoquinazolinone with (*S*)-2-acetoxypropanoyl chloride and isobutanoyl chloride, was separated into its diastereoisomers by chromatography. Reaction of one enantiopure diastereoisomer with racemic 1-phenylethylamine gave a 3·6:1 ratio of amide diastereoisomers **5** and hence this DAQ **4** diastereoisomer reacts preferentially with one enantiomer of the amine bringing about partial kinetic resolution.[2]



4

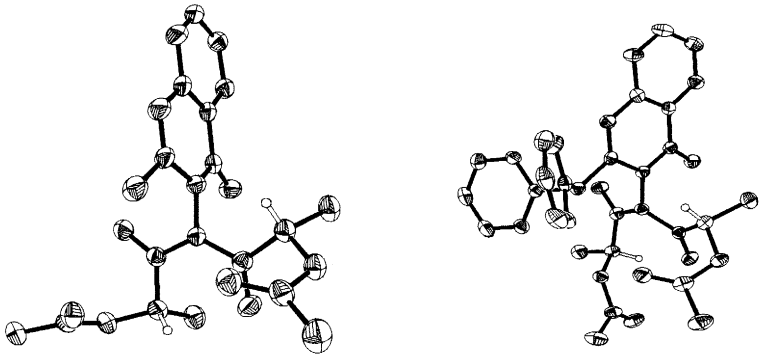
The use of an enantiopure DAQ e.g. **6a** bearing two identical chiral acyl substituents would be advantageous for kinetic resolution of amines since separation of diastereoisomers would not be required. However, since *exo/endo–endo/exo* imide interconversion **6a**⇌**6b** is expected to be fast on the timescale of the reaction with amines, the N–N bond is not a chiral axis (**6a** and **6b** have opposite configurations for their N–N chiral axes). Though kinetic resolution of chiral racemic amines with **6a**/**6b** might still be feasible, our experience is that the presence of the N–N bond as a chiral axis is required for high levels of enantioselectivity.[3]

The three DAQs **7**, **8** and **9** have been prepared by diacylation of the appropriate 3-aminoquinazolinone with (*S*)-2-acetoxypropanoyl chloride and pyridine: unexpectedly, the formation of DAQ **9** proceeded faster and in better yield (87%) than that of DAQs **7** or **8**.



7 R = Me
8 R = Pr^{i}
9 R = Ph_2CH

Crystal structures[4] of DAQs **7** and **9** (Fig. 1) show the expected (*S*)-configuration at both chiral centres in the two *N*-acyl groups. The *exo/endo* conformation for the imide is present in each case and this is expected to be the preferred conformation in solution also.



7 **9**

Fig. 1. The molecular structures of **7** and **9**: H atoms on chiral centres are shown with open bonds, all other H atoms are omitted for clarity

The NMR spectrum of DAQ **8** shows the C*H*(OAc)CH_3 signals as two quartets at δ 4·48 and 5·92 ppm and the corresponding methyl proton signals CH(OAc)CH_3 at δ 1·10 and 1·60 ppm. Likewise, the corresponding signals for DAQs **7** and **9** are comparably different in chemical shift. In contrast to the temperature dependence of the NMR spectrum of DAQ **3**, there was no change or even broadening of the C*H*(OAc)CH_3 signals in DAQs **7** and **8** down to −50°C in $CDCl_3$. Thus, fast *exo/endo–endo/exo* conformational interconversion of the imide in DAQs **7** and **8** in solution at room temperature is not occurring.[5]

In the equilibrium DAQ **6a**⇌**6b** it is important to note that, because of the absence of N–N bond rotation, the two species are diastereoisomeric and hence could differ in energy. The NMR spectra of DAQs **7**, **8** and **9** above are consistent with the presence of only one diastereoisomeric form in solution, presumably that present in the crystal form in **7** and **9**. If these *exo*/*endo* conformations are also the only reacting ones then selective reaction with one enantiomer of a racemic amine is in prospect because the N–N bonds are chiral axis (contrast **6a**⇌**6b** above).

Even under conditions of stoichiometry, DAQ **7** (1 equiv.) reacts with 2-methylpiperidine (2 equiv.) in dichloromethane at 0°C to give a 5:1 ratio of diastereoisomers of *N*-[(*S*)-2-acetoxypropanoyl]-2-methylpiperidine (76%): reaction of DAQ **9** with 2-methylpiperidine under the same conditions gave *N*-[(*S*)-2-acetoxypropanoyl]-2-(*S*)-methylpiperidine **10** (86%) as the major product (dr 33:1) corresponding to an ee of 94%.[6] Reaction of DAQ **9** with excess racemic 1-phenylethylamine gave an 8:1 ratio of amide diastereoisomers (ee 78%).[7] Unreacted amine is removed in the work-up by extraction with hydrochloric acid and amide product separated from the (re-usable) *N*-monoacyl-quinazolinone by chromatography: modification of the DAQ used to avoid the necessity for this chromatography is under investigation.

Acknowledgements

We thank the Ministry of Education in Saudi Arabia for funding (to A.G.Al-S).

References

1. Atkinson, R. S.; Barker, E.; Sutcliffe, M. J. *J. Chem. Soc., Chem. Commun.* **1996**, 1051.

2. Atkinson, R. S.; Barker, E.; Edward, P. J.; Thomson, G. A. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1047: see, previous paper in this issue, Al-Sehemi, A. G.; Atkinson, R. S.; Fawcett, J.; Russell, D. R. *Tetrahedron Lett.* **2000**, *41*, 2239.
3. We have prepared *N*-[(*S*)-2-acetoxypropanoyl]-*N*-acylaminophthalimides (which have no chiral axis) and have obtained no kinetic resolution in reaction with amines.
4. X-Ray crystallography data for **7**: $C_{19}H_{21}N_3O_7$, M=403.4, orthorhombic, space group $C222_1$, a=10.317(3), b=12.483(3), c=31.820(7) Å, V=4098(2) Å^3, Z=8, μ(Mo-Kα)=0.101 mm^{-1}, 3659 reflections measured, 3242 unique (Rint=0.028) which were all used in calculations. Final $R1$=0.051 and $wR2$=0.128 (all data). Data for **9**: $C_{31}H_{29}N_3O_7$, M=555.57, orthorhombic, space group $P2_12_12_1$, a=11.315(3), b=14.210(2), c=17.368(5) Å, V=2792(1) Å^3, Z=4, μ(Mo-Kα)=0.095 mm^{-1}, 3891 reflections measured, 3692 unique (Rint=0.029) which were all used in calculations. Final $R1$=0.102 and $wR2$=0.309 (all data). Data were measured on a Siemens P4 diffractometer at 190K using graphite monochromated Mo-Kα radiation (λ=0.7107 Å) using an ω 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 using the program SHELXTL [G. M. Sheldrick, SHELXTL version 5.1, Bruker AXS Inc., Madison, WI, 1997]. The absolute configurations of the compounds were established by the refinement of the Flack parameters. All hydrogen atoms were included in calculated positions (C–H=0.96 Å) using a riding model. All non-hydrogen atoms were refined with anisotropic displacement parameters.
5. The NMR spectrum of DAQ **9** is temperature dependent but is not compatible with fast *exo/endo–endo/exo* interconversion at room temperature.
6. Reaction of DAQ **9** (1 equiv.) with racemic 2-propylpiperidine (coniine) (4 equiv.) also gave high enantioselectivity (ee 95%) (yield 70%).
7. The faster reacting enantiomers of the amines with DAQ **9** [(*S*) for 2-methylpiperidine and (*R*) for 1-phenylethylamine] were identified by NMR comparison of the major diastereoisomers formed with authentic samples prepared from reaction of each enantiomer of the respective amine with (*S*)-2-propanoyl chloride.