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Preparation of Cyclic α-(3,4-Dihydro-2-isopropyl-4-oxoquinazolin-3-yl)amino-β-ketoesters: Further Oxidation with Lead Tetra-acetate in Dichloromethane and in Methanol Leading to Ring-Expansion and Ring-Cleavage Products, Respectively

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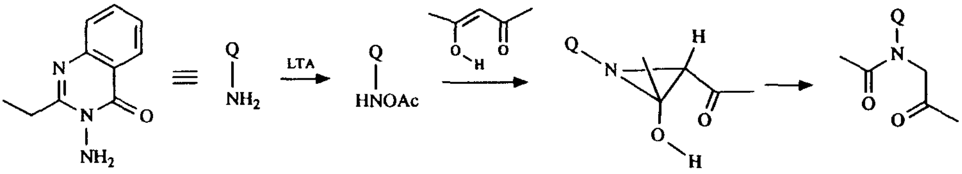
Abstract: Cyclic β-ketoesters e.g. **7** and the enol silyl ether **18** are converted to the corresponding α-(quinazolinonyl)amino (α-Q′NH) derivatives **10** and **19** respectively by reaction with the 3-acetoxyaminoquinazolinone **6**: further oxidation of **10** and **19** with lead tetra-acetate in dichloromethane gave ring-expanded products **15** and **20** respectively but with methanol as solvent the corresponding ring-cleaved products **21** and **22** are obtained: radical intermediates do not appear to be involved.

In a previous paper, we examined the reaction of e.g. 3-acetoxyaminoquinazolinone (QNHOAc) **2** with acyclic β-diketones as a route to *N*-acyl-*N*-(Q)-α-aminoketones e.g. **3** (Scheme 1).[1]

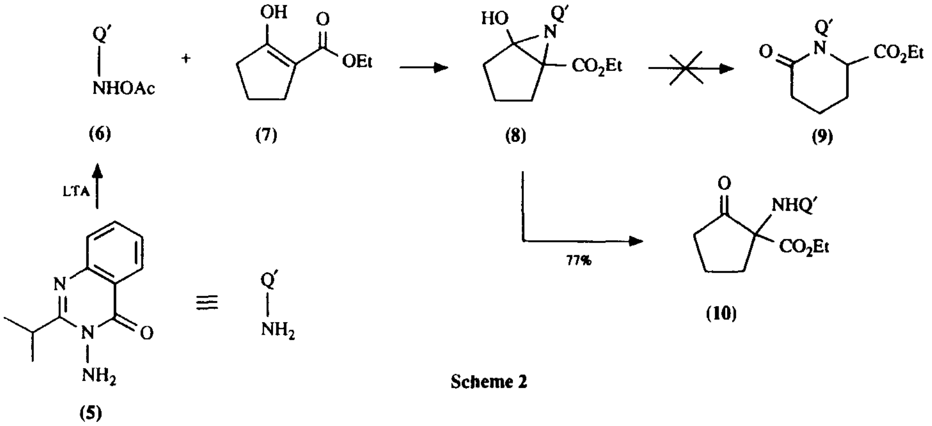
This conversion, which is analogous to that first discovered by Foucaud *et al* using oxidative addition of *N*-aminophthalimide to β-diketones,[2] involves the enolic form of the latter and ring-opening of the intermediate aziridine **4** by *C-C* bond cleavage. Simple acyclic β-ketoesters are unreactive in this reaction because of their low enol content. Compounds of type **3** are of interest because there is no rotation around the *Q-N* bond at room temperature and this bond, therefore, constitutes a chiral axis.



(1) **(2)** **(4)** **(3)**

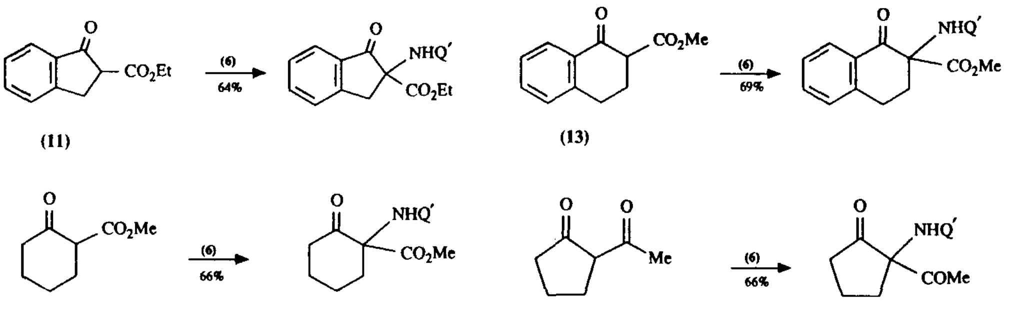
Scheme 1

We required the cyclic *N*-(Q′)-tetrahydro-α-pyridone **9** (Scheme 2) in order to study the diastereoselectivity of its alkylation α to the ester under the influence of the chiral *N-N* axis. Since cyclic β-ketoesters contain substantial amounts of enol tautomer, it appeared that **9** could be obtained in one step from the reaction of ethyl 2-oxocyclopentane carboxylate **7** with **6** *via* Foucaud-type *C-C* bond-cleavage of the intermediate aziridine **8** (Scheme 2).



Scheme 2

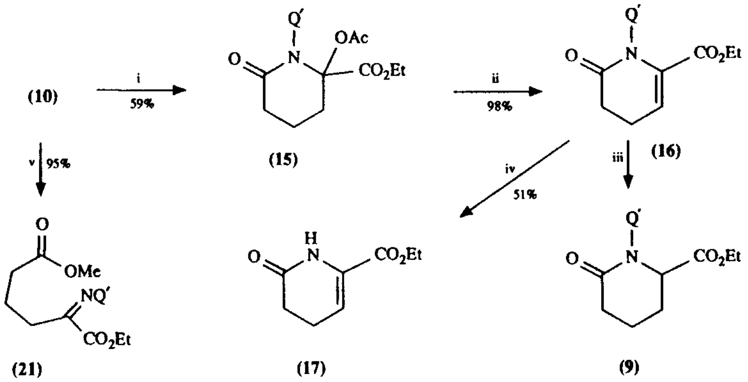
However, as shown in Scheme 2, the product from this reaction was the α-Q′NH-β-ketoester **10** m.p. 87 - 88 °C [3] arising from *C-N* rather than *C-C* bond cleavage of the intermediate aziridine **8**. This type of reaction was shown to be general for the 5- and 6-membered ring β-ketoesters **11** — **13** in Scheme 3 and also for the single cyclic β-diketone **14** that was examined.



Scheme 3

When the α-Q′NH-β-ketoester **10** was dissolved in dichloromethane and stirred with lead tetra-acetate (LTA) (1.05 mol equiv.) overnight, the major product, isolated by chromatography (59%), was identified as the α-acetoxy-ester **15** (Scheme 4). A large barrier to *Q-N* bond rotation in α-acetoxy-ester **15** would be expected and this, together with the chiral centre, means that the compound can exist in diastereoisomeric forms. However, from its ^{1}H and ^{13}C NMR spectra, **15** is clearly a single diastereoisomer.[4] Thermal elimination of acetic acid from **15** by heating at 250 °C (Kugelrohr distillation, bath temp.) gave the enamido-ester **16** m.p. 139 - 140 °C in quantitative yield.

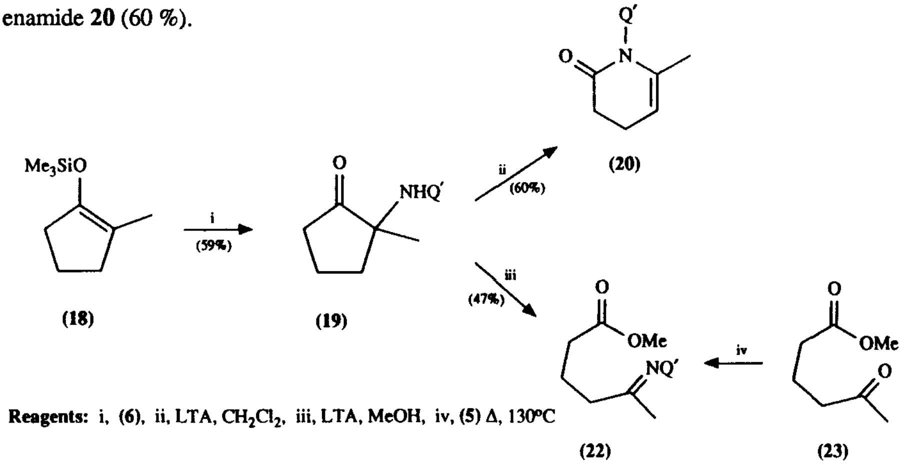
Reduction of the enamido-ester **16** with Adams catalyst gave the tetrahydro-α-pyridone **9**, the compound we originally set out to make from **7** in Scheme 2; **9** was obtained as a separable mixture (ratio 2:1) of diastereoisomers. Reduction of **16** with samarium diiodide gave the dihydro-α-pyridone **17** m.p. 54 - 55 °C in 51 % yield.



Reagents: i, LTA, CH_2Cl_2, ii, Δ, 250°C, iii, PtO_2, H_2, iv, SmI_2, Bu^{t}OH, THF, v, LTA, MeOH

Scheme 4

This ring-expansion reaction is not confined to α-Q'NH-β-ketoesters;[5] a similar reaction occurred using the ketone **19** having an α-methyl group instead of an ester. Ketone **19**, m.p. 128 - 130 °C, was prepared by reaction of **6** with the silyl enol ether **18** (Scheme 5). In this reaction, the only product isolated was the enamide **20** (60 %).



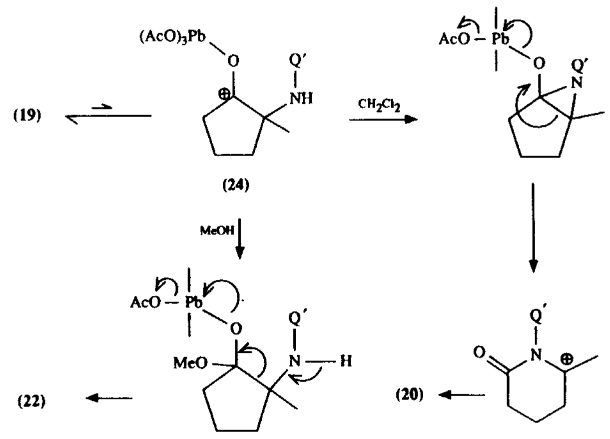
Reagents: i, (6), ii, LTA, CH_2Cl_2, iii, LTA, MeOH, iv, (5) Δ, 130°C

Scheme 5

By contrast, oxidation of **10** with LTA in *methanol* gave only the imino-diester **21** (Scheme 4) and an analogous ring-cleavage product **22** was obtained from the α-methylcyclopentanone analogue **19** (Scheme 5). Both **21** and **22** were obtained as mixtures of imine double bond isomers. An authentic sample of **22** was prepared by heating methyl 5-oxohexanoate **23** with 3-aminoquinazolinone **5**.

The formation of ring-expanded and ring-cleaved products from LTA oxidation of α-Q'NH-β-ketoester **19** can be accounted for the mechanism given in Scheme 6.

In this Scheme, the reaction is assumed to be initiated by the coordination of LTA to the ketone carbonyl.[6] The key difference in reaction course taken in the two solvents is interception of the carbocation **24** by the *solvent* in methanol, and by the relatively non-nucleophilic Q'NH in dichloromethane. Intermediates analogous to the fragmentation products **22** have been proposed in LTA oxidation of α-aminoketones but initial attack of lead (IV) on nitrogen has been proposed in this case.[7]



Scheme 6

Nitrogen-centred radical-mediated ring-expansions similar to those reported in this paper have been described[8] but there is no evidence for radical intermediates in the reactions described above; no reaction of **10** was observed on heating with α,α'azoisobutyronitrile (AIBN) (1 mol equiv.) in benzene; starting material was recovered in 72 % yield.

We thank Zeneca Specialties and SERC for support.

References and Notes

1. R.S. Atkinson, P.J. Edwards and G.A. Thomson, *J. Chem. Soc., Chem. Commun.*, 1992, 1256.
2. H. Person, K. Luanglath and A. Foucaud, *Tetrahedron Lett.*, 1977, 221.
3. All new compounds reported in this paper have been fully characterised.
4. **15** has δ^1H 0.96 (t, *J* 7.2 Hz, CH_2CH_3), 1.24, 1.46 (2 x d, *J* 6.7 Hz, CH_3CHCH_3), 1.96 - 2.09 (m, 1 H), 2.11 (s, $OCOCH_3$), 2.23 - 2.36 (m, 1 H), 2.51 - 2.59 (m, 1 H), 2.72 - 2.88 (m, 2 H). 3.17 (ddd, *J* 13.8, 10.1 and 3.5 Hz, 1 H), 3.38 (h, *J* 6.7 Hz, $(CH_3)_2CH$), 3.93 (ABX_3, CH_2CH_3), + quinaz. aromatic *H* signals. ^{13}C 12.29 (CH_2CH_3), 15.22 ($CH_2CH_2CH_2$), 20.23 (CH_3CHCH_3), 20.48 (CH_3CHCH_3), 21.53 (CH_3CO), 29.46 (CH_2), 30.03 ($(CH_3)_2CH$), 31.48 (CH_2), 61.83 (CH_2CH_3), 92.17 (*C*OAc), 119.97 (Q'*C*CO), 125.33, 125.93, 126.28, 133.73 (4 x Q'*C*H), 146.00 (Q'*C*N=C), 158.96, 162.67, 162.94 (Q'*C*=N, Q'*C*=O, CH_2CON), 167.33, 168.06 (CO_2Et and $OCOCH_3$).
5. The α-Q'NH-derivative from **11** undergoes ring-expansion (to give the isoquinolone derivative analogous to **16**) but those from **12** and **13** do not give products from ring-expansion; that from **12** undergoes the ring-cleavage reaction.
6. The formation of lead enolates by reaction of ketones with LTA is the first step in a number of oxidations with this reagent (see E.J. Corey and J.P. Schaefer, *J. Amer. Chem. Soc.*, 1960, **82**, 927.) Compounds analogous to **10** which lack the ketone carbonyl group are unreactive towards LTA in dichloromethane under the conditions used. Formation of **15** as a single diastereoisomer may indicate the intermediacy of an ester lead(IV) enolate precursor since we have previously shown that an analogous α-acetoxy carbonyl compound is obtained completely diastereoselectively from LTA oxidation of an enol under the influence of an *N-N* chiral axis (ref 1).
7. H.E. Baumgarten, D.F. McLaen and H.W. Taylor, *J. Org. Chem.*, 1971, **36**, 3668.
8. S. Kim, G.H. Joe, and J.Y. Do, *J. Amer. Chem. Soc.*, 1993, **115**, 3328.

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