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UNPRECEDENTED BASE-INDUCED RING TRANSFORMATION OF A 4-[3-AMINO-4-OXOAZETIDIN-2-YL]THIAZOL-2(3H)-ONE

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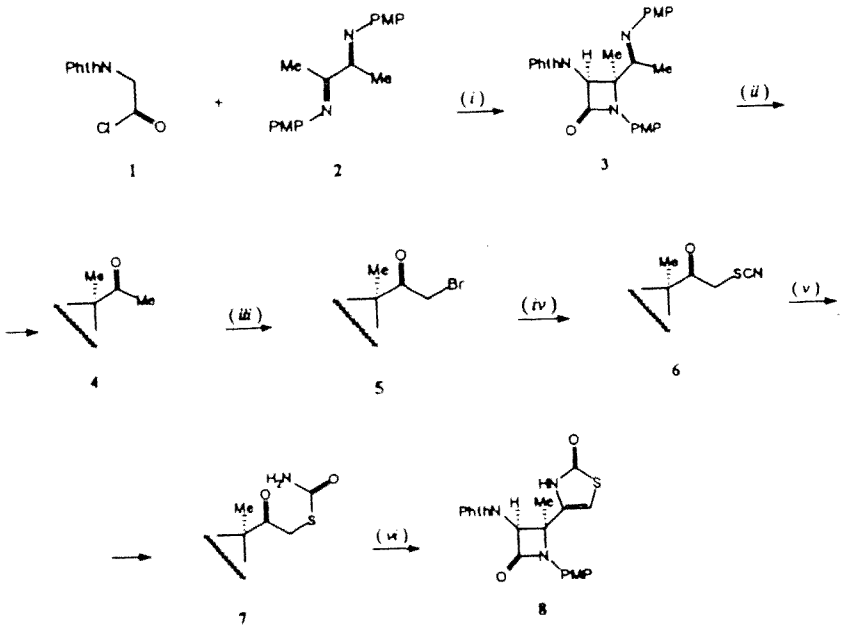
Attempted dephthaloylation 4-methyl-3-phthalimido- of 1-(p-methoxyphenyl)-4-(2'-oxo-4'-thiazolin-4'-yl)azetidin-2-one with methylhydrazine resulted in a ring transformation to give a fused thiazolo[3,4-a]pyrazine derivative.

The phthaloyl group is a popular amino-protecting group for 3-aminoazetidin-2-ones because a good hydrazinolytic method exists for the removal of the protecting group without damaging the β-lactam ring.



Scheme 1. Compounds 3-8 are racemic, only one of their enantiomers is shown. PhthN = phthalimido, PMP = 4-methoxyphenyl. (i) Et_3N. CH_2Cl_2, −20°C → room temp.; (ii) 1N HCl, MeOH, $CHCl_3$, refl.; (iii) Br_2, CH_2Cl_2, room temp.; (iv) KSCN, DMF, room temp.; (v) conc. H_2SO_4, H_2O, CH_2Cl_2, 0°C; (vi) 98% AcOH, refl.

We have now found that this dephthaloylation method does not work in the case of 3-phthalimidoazetidin-2-one **8** (whose synthesis is shown in Scheme 1) because the reagent induces an undesired concomitant ring transformation. Thus, treatment of compound **8** at room temperature with methylhydrazine in DMF afforded the expected coproduct 2-methylphthalazine-1,4-(2H,3H)-dione (**9**) and an isomer of the desired deprotection product **10**, rather than compound **10** itself. On

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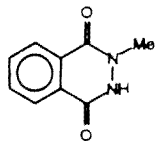
the other hand, application of an alternative mode of dephthaloylation, which avoids the use of basic reagents and conditions, namely sodium borohydride reduction of compound **8**, followed by treatment of product **11** with hydrochloric acid, afforded in addition to phthalide **12** the desired amino derivative **10**, which proved to be extremely sensitive to bases and was smoothly isomerized by aqueous NaOH or by methylhydrazine in dichloromethane to the same product which had been obtained directly from compound **8** on treatment with methylhydrazine.

In contrast, the N- and O-methyl derivatives **13** and **14** (obtained in a 1:1 ratio by treatment of compound **8** with diazomethane) which have lost the acidic NH proton of the thiazolone ring are normally dephthaloylated to afford compounds **15** and **16**, respectively, which both were found to be insensitive to bases.



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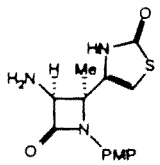
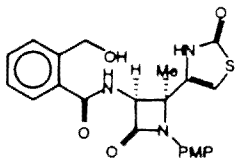
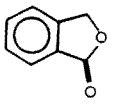


10*



11*



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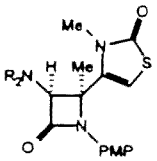
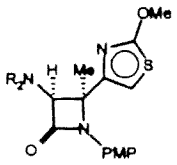
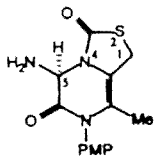


13*, **15***

13 : R_2N = PhthN (43%)
14 : R_2N = PhthN (43%)
15 : R_2N = H_2N (89%)
16 : R_2N = H_2N (75%)



14*, **16***



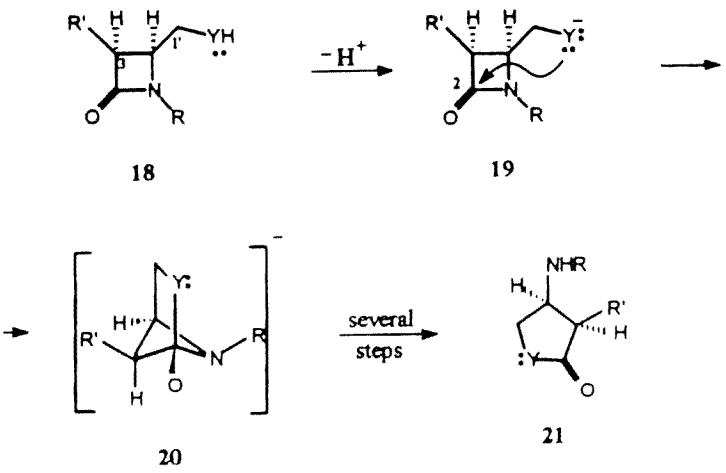
17*

These observations indicate that methylhydrazine not only brings about dephthaloylation of compound **8** but, in addition, subsequent base-catalyzed rearrangement of the resulting compound **10** as well. Support for the assumption that the order of the two events is as stated comes from the observation that compound **8** does not undergo rearrangement on treatment with potassium t-butoxide in diethyl ether or *t*-butanol, nor does it on treatment with DBU, i.e., that rearrangement does not take place without previous dephthaloylation.

Structure **17** for the product obtained on treatment of compounds **8** and **10** with methylhydrazine or of the latter with aqueous sodium hydroxide has been derived mainly from the IR and ^{1}H NMR spectra. Thus, the IR spectrum displays two amide I bands, both below 1700 cm^{-1}, which demonstrates the absence of a β-lactam ring. The ^{1}H NMR spectrum, on the other hand, shows the presence of CH_2 and NH_2 groups and the disappearance of the NH−CO group of the starting compounds **8** and **10**. Furthermore, long-range coupling and a significant NOE were observed between the methyl and methylene protons, together with less distinct NOEs between the methyl protons and the aromatic protons of the PMP group.

Comparing the structures of compounds **10** and **17** reveals that formation of the latter is the result of bond formation between C-3 of the β-lactam ring and the thiazole nitrogen atom, cleavage of the C-3−C-4 bond of the β-lactam ring, double bond migration, loss of hydrogen from a nitrogen atom, and capture of a hydrogen atom by a thiazole carbon atom.

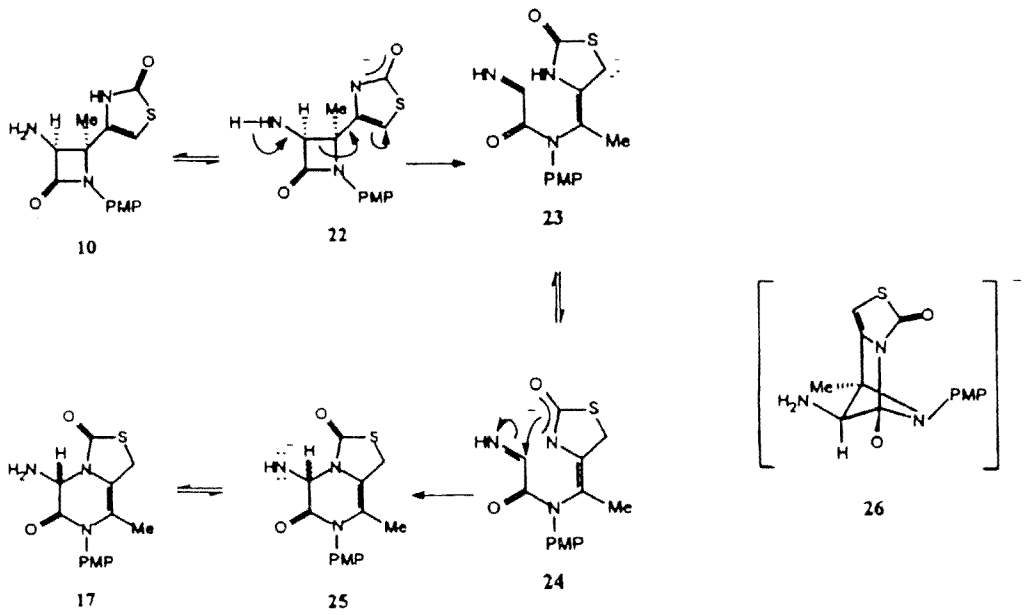
Conversion **10** → **17** is remarkable (i) because of the site of cleavage of the β-lactam ring and (ii) because of bond formation between C-3 and the nucleophilic center of the 4-substituent separated by one atom from C-4 of the β-lactam ring. Although the β-lactam ring is known to undergo easy ring fission under a variety of conditions, cleavage usually takes place at one of the bonds originating at the lactam nitrogen atom; and cleavages of the 3,4 bond not accompanied by simultaneous cleavage of the 1,2 bond are rare.



Scheme 2. Y = O, NR″.

On the other hand, many acid and base catalyzed reactions are known in which ring transformations of β-lactams are initiated by an attack of a side chain nucleophilic center (an O or N atom) separated by one atom from C-4 of the β-lactam ring. But, as shown for the base-catalyzed version of this rearrangement in Scheme 2, and in contrast to our case, it is invariably C-2 rather than C-3 of the β-lactam ring which is involved in bond formation with the nucleophilic center. *What are, then, the factors which, in our case, prompt the side chain nucleophilic center to attack C-3 of the β-lactam ring?*

The mechanism suggested for rearrangement **10** → **17** is shown in Scheme 3. The key step in rearrangement of initially formed anion **22** into carbanion **23**, comprising deprotonation of the 3-amino group and rupture of the C-3−C-4 bond of the β-lactam ring, which are thought to take place concertedly [sic]. Attack of the thiazole nitrogen of anion **22** at C-2 of the β-lactam ring (which, as mentioned before, would be the usual mode of reaction) could, in principle, set the stage for an alternative course of the reaction. However, the resulting intermediate (or transition state) **26** would still contain a strained four-membered ring and would, therefore, probably be destabilized relative to carbanion **23** whose carbanionic center is doubly stabilized by the neighboring olefinic bond and sulfur atom, and which, at the same time, is rid of the ring strain associated with the presence of a four-membered ring in the isomeric anion **26**.



Scheme 3. PMP = 4-methoxyphenyl.

Since, as a result both of N- and O-methylation of the thiazolone moiety, the acidic proton of the latter is lost, neither of the methyl derivatives is able to form anions related to **22**; therefore, as has been observed, both methyl derivatives are normally dephthaloylated by treatment with methylhydrazine.

From the mechanism shown, the crucial role of the amino and the N-unsubstituted oxodihydrothiazol-4-yl group, i.e., of both substituents attached to C-3 and C-4 respectively of the β-lactam ring, in making the ring transformation possible becomes clear. It remains to further studies to establish the scope of the new rearrangement, i.e., whether analogous rearrangements may take place if the C-3 and/or C-4 substituents of compound **10** are replaced by other suitable ones, and what the structural requirements concerning these substituents are.