Tetrahedron Letters,Vol.28,No.52,pp 6577-6580,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

2-ARYL-1,2-DIAZETIDIN-3-ONES (AZA-β-LACTAMS) VIA GRIGNARD-INDUCED CYCLIZATION OF α-(2-ARYLHYDRAZINO)-ESTERS

Joachim G. Schantl* and Martin Decristoforo

Institut für Organische und Pharmazeutische Chemie,
Universität Innsbruck, Innrain 52a, A-6020 Innsbruck, Austria

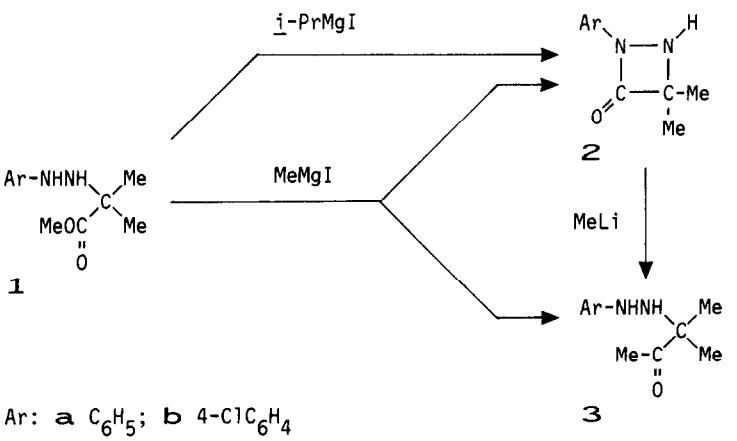
John J. Daly

Abt. ZFE, F. Hoffmann-La Roche & Co., AG., CH-4002 Basel, Switzerland

Abstract - The α-(2-arylhydrazino)-esters **1** react with i-propylmagnesium iodide to furnish 2-aryl-1,2-diazetidin-3-ones **2**, which in turn undergo ring-opening with methyllithium affording α-(2-arylhydrazino)-ketones **3**.

As part of a program to study α-(2-arylhydrazino)-alkanone arylhydrazones[1] the synthesis of α-(2-arylhydrazino)-ketones was devised, and thereby a novel access to the four-membered heterocyclic system of 1,2-diazetidin-3-ones (aza-β-lactams) was found.

Following standard procedures the 2-arylhydrazino isobutyric esters **1** are readily available starting compounds containing the required 1,2-disubstituted hydrazine moiety as has been unambiguously proved by the conversion into the corresponding arylazo ester[2]. The reaction of the esters **1** with Grignard compounds was anticipated to provide the desired α-(2-arylhydrazino)-ketones. In fact, the reaction of the esters **1** with methylmagnesium iodide furnished a mixture of two products (ratio 1:4): Beside the methylketones **3**, the 1,2-diazetidin-3-ones **2** were formed predominantly.



Ar: **a** C_6H_5; **b** 4-ClC_6H_4

The Grignard reagent employed in excess is likely to form the anion at the arylsubstituted nitrogen atom of the arylhydrazino group of **1**, thus initiating the intramolecular attack (4-exo-trig) at the carbomethoxy group[3]. Remarkably, magnesium as the counterion appears to be essential in order to accomplish the ring closure, other bases, e.g. NaH did not yield a heterocyclic product.[2] The known effect of the geminal methyl groups[4] probably assists the ring closure to furnish the 1,2-diazetidin-3-ones **2**.[5] Since the renewed treatment of **2** with methylmagnesium iodide did not bring about the ring-opening of **2** and the formation of the methylketones **3**, it became evident that the two products **2** and **3** result from competing reaction pathways. Methylmagnesium iodide effected the conversion of the esters **1** into the methylketones **3**, but only to a minor extend. The sterically more demanding i-propylmagnesium iodide fully suppressed the ketone formation, the sole products isolated in good yields were the 1,2-diazetidin-3-ones **2**.

Whereas azetidin-2-ones (β-lactams) have been intensively investigated, the nuclear analogues, the 1,2-diazetidin-3-ones (aza-β-lactams) have attracted some interest only recently.[6,7] The most widely used synthetic route to this four-membered ring involves [2+2]-cycloaddition reactions,[8] but also ring contractions[6,8] of higher-membered heterocycles as well as intramolecular ring-closure reactions[8,9] have been applied. The formation of compounds **2** reported herein adds to the latter category of synthesis, and it offers access to the less known N1-unsubstituted derivatives.

The solution of **1** (0.12 mol) in ether (80 ml) was added at -10°C within 5 min to a stirred solution of 2-propylmagnesium iodide, prepared from magnesium (9.5 g, 0.39 mol) and 2-iodopropane (71.7 g, 0.42 mol) in dry ether (80 ml) under N_2-atmosphere. After the evolution of propane has ceased the mixture was warmed to 20°C, and a saturated aqueous solution of ammonium chloride was added dropwise. The ether layer was washed (H_2O), dried (Na_2SO_4), and concentrated; the residue was recrystallized from methylcyclohexane to give colorless crystals: 16.9 g (80%) **2a**; 20.2 g (80%) **2b**.[10,11]

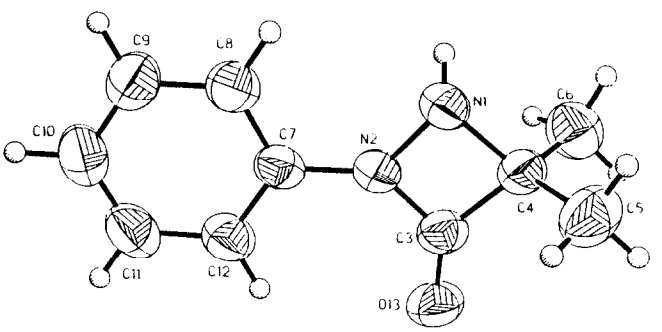


Fig. 1. ORTEP-drawing of **2a**

The X-ray structure analysis of **2a** (Fig. 1)[12] indicates the nonplanar four-membered ring structure with a folding angle of 6.1° along N1···C3.[14]

The ring inversion of 1,2-diazetidines at ambient temperatures has been reported to be fast on the NMR time scale.[15] Therefore, the nonequivalence of the geminal methyl groups at C4 of **2**, as revealed by the ^1H NMR at 40°C, is attributed to the comparatively slow inversion of the sp^3 hybridized N1-atom.[16] The two signals of the diastereotopic methyl groups coalesce upon addition of traces of acid. The two amide carbonyl absorptions[11] displayed in the IR of **2** presumably originate from diastereomeric ring- and N1-invertomers (two pairs of enantiomers are envisaged) owing to the syn and anti position of the N1-H-bond with respect to the carbonyl group across the nonplanar ring.[17]

The ring-opening of the 1,2-diazetidin-3-ones **2** was readily achieved by the use of methyllithium.[19] The cleavage of the C3-N2 amide bond gives rise to the formation of 3-(2-arylhydrazino)-3-methyl-2-butanones **3**.

To a solution of **2** (4.25 mmol) in dry ether (20 ml) at -20°C under N_2-atmosphere was added a solution of methyllithium (1.6 molar) in ether (10 ml) within 1 min. The initially formed precipitate dissolved after 20 min stirring, and water (10 ml) was added dropwise to the redbrown solution. The organic phase was separated, washed (H_2O), and dried (Na_2SO_4), and the solvent was removed to give **3**:[20] The oily **3a** crystallized from pentane (40 ml) at -50°C: 0.58 g (71 %); **3b** was recrystallized from methanol/water: 0.75 g (78 %).

REFERENCES AND NOTES

1. J.G. Schantl, P. Karpellus, and M. Prean, Tetrahedron 38 (1982) 2643.
2. M. Decristoforo, Dissertation, University of Innsbruck, 1987.
3. This ring-closure is related to the facile aminolysis and hydrolysis of β-ketoesters by intramolecular catalysis via the formation of an intermediate four-membered lactam and lactone, respectively: M. Labelle and D. Gravel, J. Chem. Soc., Chem. Commun. (1985) 105; W.N. Washburn and E.R. Cook, J. Am. Chem. Soc. 108 (1986) 5962.
4. N.L. Allinger and V. Zalkow, J. Org. Chem. 25 (1960) 701.
5. The cyclization of **1** parallels the conversion of β-aminoesters into azetidin-2-ones (β-lactams): R. Breckpot, Bull. Soc. Chim. Belg. 32 (1923) 412.
6. G. Lawton, C.J. Moody, C.J. Pearson, and D.J. Williams, J. Chem. Soc. Perkin Trans. I (1987) 885.
7. E.C. Taylor, H.M.L. Davies, and J.S. Hinkle, J. Org. Chem. 51 (1986) 1530.
8. Reviews: a) R. Richter and H. Ulrich in A. Hassner (ed): Small Ring Heterocycles, Part 2, Wiley, New York 1983, p 443. b) J.W. Timberlake and E.S. Elder in A.R. Katritzky, C.W. Rees, and W. Lwowski (ed): Comprehensive Heterocyclic Chemistry, Vol. 7, Pergamon Press, Oxford 1984, p 449.
9. E.C. Taylor, N.F. Haley, and R.J. Clemens, J. Am. Chem. Soc. 103 (1981) 7743.
10. Satisfactory elemental analyses were obtained for all new compounds.

11. **2a**: mp 83-84°C. IR (KBr): 3200 (NH), 1735, 1720 cm^{-1} (C=O); IR ($CHCl_3$): 1760, 1745 cm^{-1} sh (C=O). ^1H NMR (60 MHz, CCl_4): δ 1.40 and 1.52 (2s, CH_3), 4.29 (s, NH), 6.7-7.2 (m, C_6H_5). MS (75 eV): m/e 176 (17%, $M^{+\cdot}$).
2b: mp 70°C. IR (KBr): 3210 (NH), 1755 sh, 1730 cm^{-1} (C=O); IR ($CHCl_3$): 1765, 1750 cm^{-1} sh (C=O). ^1H NMR (CCl_4): δ 1.42 and 1.55 (2s, CH_3), 4.40 (s, NH), 7.07 (s, 4-ClC_6H_4). MS (75 eV): m/e 210 (23%, $M^{+\cdot}$).

12. Crystal data of **2a**: Space group and cell dimensions: Monoclinic, $P2_1/n$ with a=9.616(20), b=10.301(15), c=10.502(19)Å, β=107.92(15)°; density D=1.182 Mgm^{-3}, Z=4. Data collection (Nicolet R3m four-circle diffractometer, $Mo_{K\alpha}$, graphite monochromator). Crystal size: 0.14 x 0.40 x 0.24mm^3; temp.: 295K; wavelength: 0.71069Å; total data measured: 1964 (excluding standards), total data observed: 990. The structure was determined by direct methods using 32 starting phase permutations. Refinement proceeded smoothly to convergence at R=0.0447 with anisotropic refinement of all non-H-atoms. (SHELXTL program package, version number 4).[13]
Coordinates and thermal parameters for all compounds have been deposited with the Crystallographic Data Centre, Cambridge University, University Chemical Laboratory, Cambridge CB2 1EW, England.

13. G.M. Sheldrick, University of Göttingen, 1983.

14. Selected structural data of **2a**: Bond lengths [Å]: N1-N2 1.462(4), N2-C3 1.352(3), C3-C4 1.515(4), N1-C4 1.525(3), N2-C7 1.398(4), C3-O13 1.212(3), C4-C5 1.514(4), C4-C6 1.505(4). Bond angles [°]: N1-N2-C3 95.7(2), N2-C3-C4 90.9(2), N1-C4-C3 86.7(2), N2-N1-C4 86.4(2), N1-N2-C7 125.6(2), C3-N2-C7 137.5(2), N2-C3-O13 131.7(3), C4-C3-O13 137.3.

15. J.H. Hall and W.S. Bigard, J. Org. Chem. 43 (1987) 2785; S.F. Nelsen, V.E. Peacock, G.R. Weisman, M.E. Laudis, and J.A. Spencer, J. Am. Chem. Soc. 100 (1978) 2806.

16. A. Mannschreck, V. Jonas, and B. Kolb, Angew. Chem. 85 (1973) 590; Angew. Chem. Int. Ed. Engl. 12 (1973) 583, and lit. cited therein.

17. Also 1-alkylsubstituted 1,2-diazetidinones exhibit two carbonyl absorptions.[2,9] The two carbonyl frequencies of 1-unsubstituted and 1-alkyl-1,2-diazetidinones are lower than the ring-carbonyl frequency of 1-acyl- and 1-aryl derivatives.[8,18]

18. C.W. Bird, J. Chem. Soc. (1963) 674.

19. The reaction of organolithium compounds with 1,2,4,4-tetraphenyl-1,2-diazetidin-3-one is reported to result in the cleavage of the N-N- and C-C-bonds of the heterocycle: J.H. Hall, J. Org. Chem. 29 (1964) 3188.

20. **3a**: mp 44-46°C. IR (KBr): 3330 (NH), 1690 cm^{-1} (C=O). ^1H NMR ($CDCl_3$): δ 1.30 (s, $(CH_3)_2C$), 2.14 (s, CH_3CO), 4.05 (s, C-NH-N), 5.40 (s, N-NH-Ar), 6.5-7.3 (m, C_6H_5).
3b: mp 150°C. IR (KBr): 3330 (NH), 1695 cm^{-1} (C=O). ^1H NMR ($CDCl_3$): δ 1.30 (s, $(CH_3)_2C$), 2.16 (s, CH_3CO), 3.6-4.6 (s, br, NH), 5.4 (s, br, NH), 6.66, 6.82, 6.98, 7.13 (AA'BB', 4-ClC_6H_4).

(Received in Germany 5 August 1987)