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Highly Diastereoselective Ring Chain Transformation of Butenolides to 5-(α-Hydroxyalkyl)pyrazolidin-3-ones[1]

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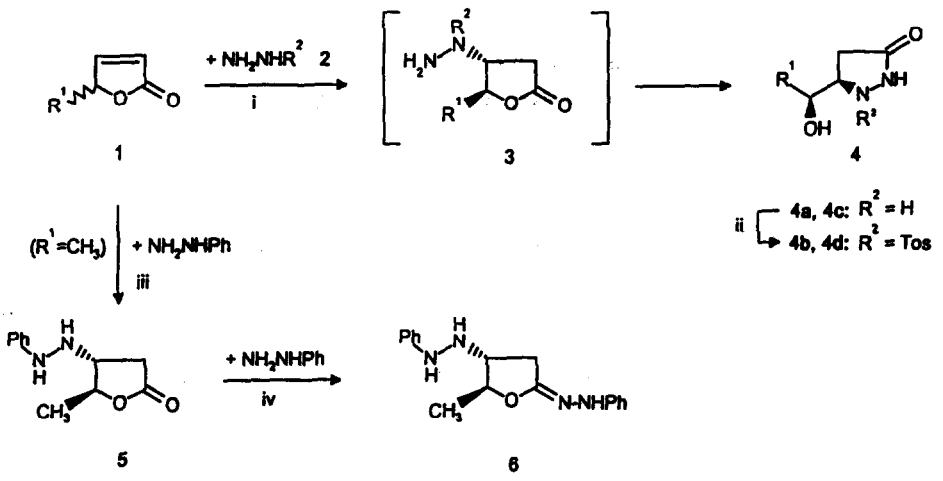
Abstract: Butenolides 1 react with hydrazines 2 by a novel ring chain transformation to 5-(α-hydroxyalkyl)pyrazolidin-3-ones 4 via intermediate 4-hydrazinobutyrolactones 3 in a highly diastereoselective manner.

Ring chain transformations with bridged 1,3-dicarbonyl heteroanalogues represent a useful method for the synthesis of a variety of ω-aminoalkylheteroaromatics.[2,3] For example, 2-aroylmethylidenepyrrolidines or corresponding 3-chloropropeniminium salts react as 1,3-bi-electrophiles with hydrazine giving ω-aminopropylpyrazoles.[3]

We became interested in extending this concept to bridged α,ß-unsaturated carbonyl compounds as reactants in order to synthesize partially saturated heterocycles in a stereoselective manner.

As a first example we report a ring chain transformation of butenolides 1 with hydrazines 2. If hydrazine or methylhydrazine 2 (R^2 = H or CH_3) is reacted with butenolides 1 in a polar solvent 5-(α-hydroxyalkyl)pyrazolidin-3-ones 4 are obtained in high chemical yields and high diastereomeric excess. If the enantiomerically pure starting material 1 (R^1 = CH_2OH) was used, only one optical isomer 4c was isolated. Usually traces of 4-hydrazinobutyrolactones 3 are found in the reaction mixture. Kinetic studies (to be reported elsewhere) revealed that these compounds 3 act as intermediates in the formation of the pyrazolidinones 4. Consequently, the transformation of the butenolides 1 to 5-(α-hydroxyalkyl)pyrazolidin-3-ones 4 starts with the addition of the hydrazine 2 to the C-C double bond of the α,ß-unsaturated system 1. Subsequent attack of the second amino group of the hydrazine moiety at the carbonyl group of the lactone intermediate 3 results in a ring cleavage giving the products 4. If phenylhydrazine 2 (R^1 = phenyl) is used, an addition product (5) can again be observed, but the latter reacts with a second molecule of phenylhydrazine by cleaving the exocyclic



i. H_2O, 2h, 80°C. ii. DMAP, TosCl, pyridine, 2h. iii. H_2O, 10 min, 80°C. iv. ethyl acetate, 3d, r.t..

C-O bond, giving a 4-phenylhydrazinotetrahydrofuran-2-hydrazone 6, rather than undergoing a ring chain transformation. Nevertheless this result is also interesting since reaction of butenolides with two molecules of amines is known to give ring-opened 4-aminobutanamides[4] rather than 4-aminotetrahydrofuran-2-imines.

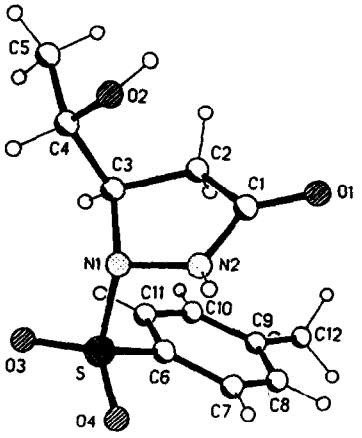


Fig. 1: X-Ray structural analysis of 4b[5]

Table 1: Preparation of 5-(α-hydroxyalkyl)pyrazolidin-3-ones **4**, 4-phenylhydrazinobutyrolactone **5**, and 4-phenylhydrazinotetrahydrofuran-2-hydrazone **6**

	R^1	R^2	yield / %	ratio of diastereomers
4a [2]	Me	H	63	86 : 14 [1]
4b [3]	Me	Tos	75	94 : 6 [1]
4c	CH_2OH (S)	H	72	>95 : 5
4d	CH_2OH (S)	Tos	30	>95 : 5
4e	Me	Me	61	>95 : 5 [1]
5a [4]	Me	Ph	15	>95 : 5 [1]
6a [5]	Me	Ph	18	90 : 10 [1]

[1] racemic

[2] ^{1}H-NMR (300 MHz, DMSO-d_6, TMS); δ / ppm ; J / Hz : 1.03 (d, 3H, J = 6)CH_3; 2.21 (dd, 1H, J_1 = 16, J_2 = 7)CH_2; 2.30 (dd, 1H, J_1 = 16, J_2 = 7)CH_2; 3.20 (q, 1H, J = 7)CH-N; 3.51 (p, 1H, J = 6) CH-O; 8.91; (sb, 1H)NH
^{13}C-NMR (75 MHz, DMSO-d_6, TMS); δ / ppm : 20.8 (CH_3); 33.2 (CH_2); 63.0 (CH-N); 66.0 (CH-O); 175.6 (C=O)
^{15}N-NMR (30 MHz, D_2O); δ / ppm : 78.9 (NH-CH); 140.0 (NH-CO)

[3] ^{1}H-NMR (300 MHz, DMSO-d_6, TMS); δ / ppm ; J / Hz : 1.11 (d, 3H, J = 6)CH_3; 1.22 (dd, 1H, J_1 = 17, J_2 = 9)CH_2; 1.99 (d, 1H, J = 17)CH_2; 2.42 (s, 3H)Ph-CH_3; 3.54 (p, 1H, J = 6)CH-O; 3.78 (t, 1H, J = 7)CH-N; 5.07 (d, 1H, J = 6)OH; 7.48 (d, 2H, J = 8)CH_{arom}; 7.74 (d, 2H, J = 8)CH_{arom}; 10.73 (s, 1H)NH
^{13}C-NMR (75 MHz, DMSO-d_6, TMS); δ / ppm : 20.1 (CH_3); 21.2 (CH_3); 29.7 (CH_2); 64.7 (CH-N); 67.1 (CH-O); 129.0 (CH_{arom}); 130.2 (CH_{arom}); 130.2 (C_{arom}); 145.4 (C_{arom}); 174.3 (C=O)
m.p. : 206-8 °C

[4] ^{1}H-NMR (300 MHz, DMSO-d_6, TMS); δ / ppm ; J / Hz : 1.25 (d, 3H, J = 7)CH_3; 2.30 (dd, 1H, J_1 = 18, J_2 = 3)CH_2; 2.82 (dd, 1H, J_1 = 18, J_2 = 7)CH_2; 3.37 (m, 1H)CH-N; 4.45 (qd, 1H, J_1 = 7, J_2 = 2)CH-O; 4.82 (sb 1H)NH; 6.90 (m, 5H)Ph; 7.62 (sb, 1H)NH-Ph
^{13}C-NMR (75 MHz, DMSO-d_6, TMS); δ / ppm : 19.0 (CH_3); 32.6 (CH_2); 60.9 (CH-N); 79.6 (CH-O); 111.8 (CH_{arom}); 117.2 (CH_{arom}); 128.7 (CH_{arom}); 145.4 (C_{arom}); 150.5 (C_{arom}); 176.1 (C=O)
m.p. : 112-4 °C

[5] ^{1}H-NMR (300 MHz, DMSO-d_6, TMS); δ / ppm ; J / Hz : 1.12 (d, 3H, J = 7)CH_3; 2.72 (dd, 1H, J_1 = 14, J_2 = 3)CH_2; 2.90 (dd, 1H, J_1 = 14, J_2 = 9)CH_2; 4.06 (m, 2H)CH-N, CH-O; 5.02 (d, 1H)NH; 6.52 (m, 3H) CH_{arom}; 6.82 (m, 2H)CH_{arom}; 7.60 (m, 6H)CH_{arom}, NH;); 9.69 (d, 1H, J = 3)NH
^{13}C-NMR (75 MHz, DMSO-d_6, TMS); δ / ppm : 20.4 (CH_3); 33.5 (CH_2); 67.5 (CH-N); 80.0 (CH-O); 112.0 (CH_{arom}); 118.0 (CH_{arom}); 122.1 (CH_{arom}); 128.3 (CH_{arom}); 129.1 (CH_{arom}); 130.7 (CH_{arom}); 149.1 (C_{arom}); 151.4 (C_{arom}); 170.1 (C=O)
m.p. : 135-7 °C

The non tosylated products **4** appeared as oils. Their spectroscopic data are in full agreement with the proposed structures. The regioselectivity of the reaction of methylhydrazine **2** (R^2 =

CH_3) with the butenolide 1 (R^1 = Me) could be proved by NOE difference ^{1}H-NMR experiments demonstrating the proximity of $R^2(CH_3)$ and the CHOH moiety in the final product 4e. The relative stereochemistry of the substituents at both chiral centers could be proved by transforming the N-unsubstituted pyrazolidin-3-one 4a to the crystalline 1-tosyl derivative 4b and X-ray crystal structure analysis.[5] The relative configuration (ul) at the two asymmetric carbon atoms implies an approach of the hydrazine 2 to the C-C double bond of 1 from the less hindered side, viz. opposite the substituent R^1. A similar stereochemical pathway is reported in the addition of amines to butenolides[4] and pentenolides.[6]

The extension of the ring chain transformation principle to other bridged 1,3-bielectrophiles (e. g. pentenolides[6] or α,ß-unsaturated lactams) or other binucleophiles is currently under way. Recently the ring chain transformation of pentenolides with hydroxylamines was reported.[7,8]

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References and Notes

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5. Compound 4b ($C_{12}H_{16}N_2O_4S$) crystallises in the triclinic space group P1 with *a* = 6.562(3), *b* = 10.352(6), *c* = 10.699(6) A, α = 110.25(3), ß = 96.91(3), γ = 95.34(3)°, *U* = 669.8A^3 (at -130°C), *Z* = 2, Mo-*Kα* radiation, $2\Theta_{max}$ 50°. The structure was solved by direct methods and refined anisotropically on F^2 (all 2354 independent reflections, H atoms using a riding model) to *wR* (F^2) 0.080 (conventional *R*(*F*) 0.033). Program system: SHELXS/L-92. Full details have been deposited at the Fachinformationszentrum Karlsruhe, Gesellschaft für Wissenschaftlich-technische Information mbH, D-7514 Eggenstein-Leopoldshafen 2, Federal Republic of Germany. Any request for this material should quote a full literature citation and the reference number CSD 56913.
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