PREPARATION OF CYCLIC α-HYDRAZINO ACIDS THROUGH *N*-ACYLHYDRAZONIUM INTERMEDIATES

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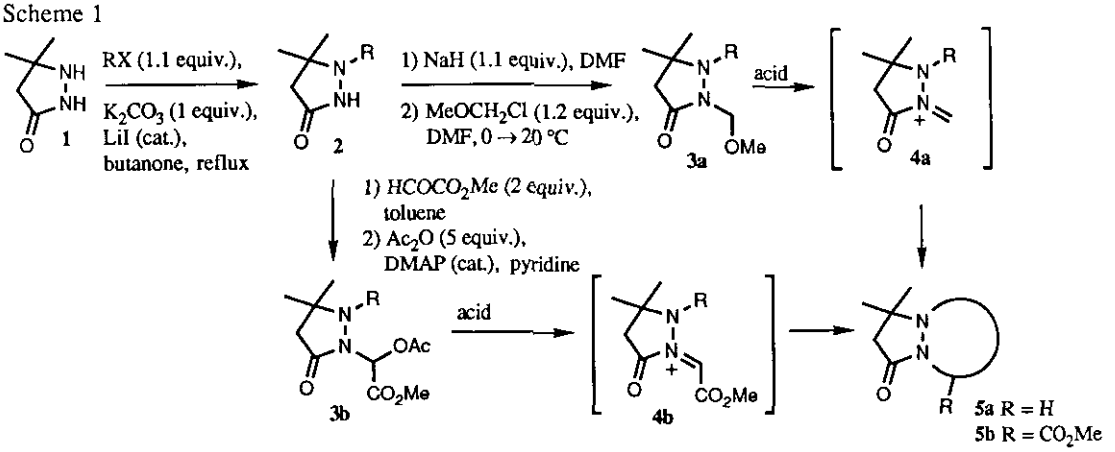
Abstract- An efficient synthesis of bicyclic hydrazine derivatives (**5a**) and (**5b**) through the intermediacy of exocyclic hydrazonium ions (**4a**) and (**4b**) is described.

Among the growing interest in the class of cyclic hydrazine compounds, special attention is paid to hydrazines containing an α-carboxyl function, the so-called α-hydrazino acid derivatives.[1] As a result of their strong resemblance to the corresponding α-amino acids, they have a promising biological potential as inhibitors of these α-amino acids and can also be converted into α-amino acids by cleavage of the N-N bond. Recently, bicyclic hydrazino acids were synthesized via an intermolecular 1,3-dipolar cycloaddition reaction[2] or via an intramolecular Wadsworth-Horner-Emmons condensation.[3]

In addition to these methods, a novel method for preparing not only bicyclic hydrazines (**5a**), but also for α-hydrazino acid derivatives (**5b**) is presented here. In conjunction with our earlier work on *N,N'*-diacylhydrazonium ions[4] and endocyclic *N*-acylhydrazonium ions,[5] the synthesis of both classes of compounds via exocyclic ringclosure of *N*-acylhydrazonium ions (**4a**) and (**4b**) is described.

Scheme 1

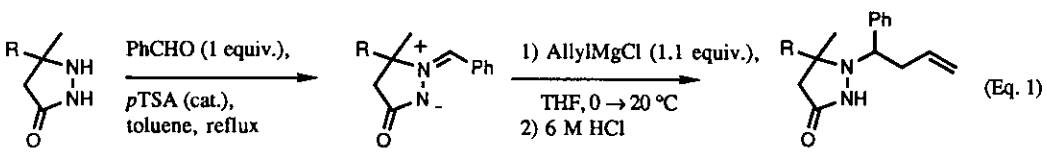


The general route that was followed is outlined in Scheme 1. Alkylation of pyrazolidone (**1**)[6] with activated alkenyl halides afforded the hydrazines (**2**).[5] Cyclization precursors (**3a**) and (**3b**) were obtained by either deprotonation with NaH, followed by alkylation with chloromethyl methyl ether, or condensation with methyl glyoxylate[7] and subsequent acetylation of the hydroxyl group with excess of acetic anhydride. Cyclization products (**5a**) and (**5b**) were obtained upon use of $TiCl_4$ (2 equiv, CH_2Cl_2, -78 → 20 °C), $BF_3{\cdot}OEt_2$ (2 equiv., CH_2Cl_2, 0 → 20 °C), or HCOOH (various temperatures).

As can be seen from the Table, the cyclizations occur in moderate to good yields.[8] In the case of a prenyl substituent (entry 2a), treatment with formic acid gave the formate (**7a**) in high yield, whereas treatment with $TiCl_4$ also gave some elimination product (**9**). In the presence of an α-methoxycarbonyl group (entry 2b), elimination product was not found, but beside the trans substituted hydrazines (**7b**) and (**8b**) considerable amounts of lactone (**10**) were formed. The trans stereochemistry of **7b** and **8b** was initially deduced from NOE difference ^1H nmr data of **8b** and confirmed later by an X-ray analysis of **8b** (the signal of the α-methine proton of **8b** (d, 4.60 ppm) showed a small coupling constant (J = 5.2 Hz), comparable with **7b** (d, J = 4.9 Hz, 4.61 ppm), whereas a large coupling constant was found for **10** (d, J = 9.1 Hz, 5.01 ppm)).

The allylsilane substituted precursors (entries 3a and 3b) afforded the 5,6-bicyclic systems (**11a**) and (**11b**) containing an exocyclic methylene substituent. In contrast, less activated nucleophiles like allyl or methallyl functions gave only very small amounts of cyclized products (less than 10%).

Activation of the hydroxyl function by converting it into an acetate was required to effect cyclization. Even in the case of the strongly nucleophilic propargylsilane (entry 4b) the hydroxy compound did not give allene (**12b**) upon treatment with acid. On the contrary, starting from compound (**2**) (R = Bn), the cyclization product (**6a**) could also be obtained (in 66% yield) in a one-pot reaction by treating **2** (R = Bn) with HCOOH in the presence of 1.5 equiv. of 1,3,5-trioxane.



1 R = Me
15 R = H

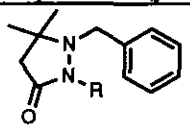
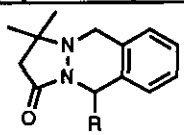
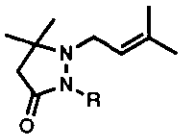
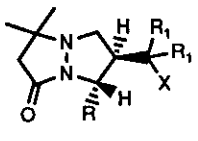
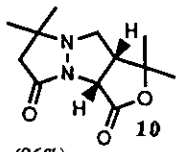
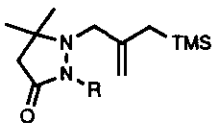
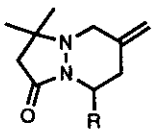
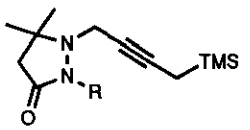
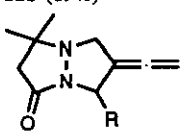
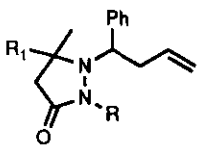
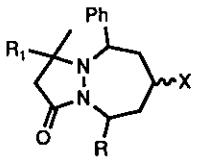
16 R = H (83%)
17 R = Me (89%)

18 R = H (82%)
19 R = Me (45%)

(Eq. 1)

Synthesis of 5,7-bicyclic systems (entries 5a and 5b) is also possible, although cyclization occurs in rather

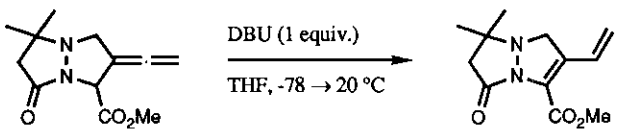
Table

entry	precursor (yield)[a]	acid	cyclization product(s) (yield)
			
1a	R = CH_2OMe (69%)	$HCOOH$[b]	**6a** R = H (52%)
		$TiCl_4$	**6a** (98%)
1b	R = $CH(OAc)CO_2Me$ (57%)	$HCOOH$[b]	**6b** R = CO_2Me (33%)
		$TiCl_4$	**6b** (68%)
			 
2a	R = CH_2OMe (29%)	$HCOOH$[c]	**7a** R = H, X = OCHO, R_1 = Me (96%)
		$TiCl_4$	**8a** R = H, X = Cl, R_1 = Me (76%); **9** R = H, X = Me, $R_1 = R_1 = =CH_2$ (17%)
2b	R = $CH(OAc)CO_2Me$ (80%)	$HCOOH$[d]	**7b** R = CO_2Me, X = OCHO, R_1 = Me (53%); **10**[f] lactone (18%)
		$TiCl_4$	**8b** R = CO_2Me, X = Cl, R_1 = Me (36%); **10**[f] (20%)
			
3a	R = CH_2OMe (42%)	$HCOOH$[e]	**11a** R = H (91%)
		$BF_3{\cdot}OEt_2$	**11a** (71%)
3b	R = $CH(OAc)CO_2Me$ (55%)	$HCOOH$[e]	**11b** R = CO_2Me (21%)
		$BF_3{\cdot}OEt_2$	**11b** (69%)
			
4a	R = CH_2OMe (22%)	$HCOOH$[e]	**12a** R = H (94%)
		$BF_3{\cdot}OEt_2$	**12a** (88%)
4b	R = $CH(OAc)CO_2Me$ (61%)	$HCOOH$[e]	**12b** R = CO_2Me (54%)
		$BF_3{\cdot}OEt_2$	**12b** (68%)
			
5a	R = CH_2OMe, R_1 = H (50%)[g]	$HCOOH$[d]	**13a** R = H, R_1 = H, X = OCHO (53%) (4.6 : 1 ratio of diastereomers)
5b	R = $CH(OAc)CO_2Me$, R_1 = Me (31%)[g]	$HCOOH$[c]	**13b** R = CO_2Me, R_1 = Me, X = OCHO (14%, one diastereomer)
		$SnCl_4$	**14b** R = CO_2Me, R_1 = Me, X = Cl (18%, one diastereomer)

a) Isolated yield after two steps. b) Reaction mixture was stirred for 17 h at 50 °C. c) Reaction mixture was stirred for 17 h at 25 °C. d) Reaction mixture was stirred for 40 h at 25 °C. e) Reaction mixture was stirred for 5 h at 25 °C. f) **10** could not be separated from the other product by flash chromatography. g) Isolated yield after three steps.

low yields. In these cases the precursors were obtained by condensation of pyrazolidones (**1**) and (**15**) with benzaldehyde (Eq. 1), yielding the stable ylides **16** and **17**[9] that could be alkylated with allylmagnesium chloride to give **18** and **19**. After functionalization at N-2, treatment with acid afforded only 7-membered ring systems. Cyclization at the phenyl group was not observed.

As an application of this method, allene (**12b**) was converted (by using 1 equiv. of DBU) into the conjugated system (**20**) (Eq. 2), which strongly resembles some biologically active hydrazine systems.[2,3]



12b **20** 20%

(Eq. 2)

In conclusion, the use of exocyclic hydrazonium ions (**4a**) and (**4b**) provides an efficient route for synthesizing various functionalized bicyclic hydrazines and α-hydrazino acids. At the moment, additional applications of these hydrazonium intermediates and their reaction products are actively explored.

ACKNOWLEDGEMENT

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7. H. H. Mooiweer, H. Hiemstra, H. P. Fortgens, and W. N. Speckamp, *Tetrahedron Lett.*, 1987, 28, 3285. Reaction with anhydrous methyl glyoxylate (generated from the commercially available methyl hemiacetal of methyl glyoxylate through distillation from phosporus pentoxide (cf. J. M. Hook, *Synth. Comm.*, 1984, 14, 83) occurs equally well.

8. All new products were appropriately characterized by ir, ^{1}H nmr, ^{13}C nmr and accurate mass measurements. The spectral data corresponded to the given structures. Some selected data: **8b**: mp 91-93 °C (EtOAc/hexane 1:5); ir (ν, cm^{-1}, $CHCl_3$) 1750, 1710; ^{1}H nmr (δ, ppm, $CDCl_3$, 200 MHz) 1.32 (s, 3 H, NCC*H*$_3$CH$_3$), 1.35 (s, 3 H, NCCH$_3$C*H*$_3$), 1.52 (s, 3 H, CClC*H*$_3$CH$_3$), 1.61 (s, 3 H, CClCH$_3$C*H*$_3$), 2.31 (d, *J* = 17.3 Hz, 1 H, NCC*H*H), 2.54 (d, *J* = 17.3 Hz, 1 H, NCCH*H*), 2.64 (dd, *J* = 9.4, 8.0 Hz, 1 H, NC*H*H), 3.03-3.11 (t, *J* = 8.0 Hz, 1 H, NCH*H*, and ddd, *J* = 5.3, 7.8, 9.5 Hz, 1 H, NCH$_2$C*H*), 3.73 (s, 3 H, OCH$_3$), 4.60 (d, *J* = 5.2 Hz, 1 H, NCH); ^{13}C nmr (δ, ppm, $CDCl_3$, 50 MHz) 23.5 (NC*C*H$_3$CH$_3$), 29.1 (NCCH$_3$*C*H$_3$), 31.5 (CCl*C*H$_3$CH$_3$), 32.0 (CClCH$_3$*C*H$_3$), 41.7 (C(O)*C*H$_2$), 51.0 (NCH$_2$), 52.8 (OCH$_3$), 56.9 (N*C*(CH$_3$)$_2$), 57.5 (NCH$_2$*C*H), 57.8 (NCH), 69.9 (CCl), 171.0 (C(O)), 176.8 (C(O)); ms (m/z) 288 ($M^{+\cdot}$), 273, 114, 99, 43; Accurate mass 288.1205 (Calcd for $C_{13}H_{21}N_2O_3Cl$ 288.1240); **12b** (colorless oil): ir (ν, cm^{-1}, $CHCl_3$) 1960, 1730, 1700; ^{1}H nmr (δ, ppm, $CDCl_3$, 200 MHz) 1.32 (s, 3 H, CC*H*$_3$CH$_3$), 1.43 (s, 3 H, CCH$_3$C*H*$_3$), 2.45 (d, *J* = 17.2 Hz, 1 H, NCCH*H*), 2.54 (d, *J* = 17.2 Hz, 1 H, NCC*H*H), 3.34 (dt, *J* = 4.0, 11.2, 1 H, NCH*H*), 3.59 (dt, *J* = 11.2, 2.1 Hz, 1 H, NC*H*H), 3.76 (s, 3 H, OCH$_3$), 5.02-5.08 (m, 3 H, C=CH$_2$ + NCH); ^{13}C nmr (δ, ppm, $CDCl_3$, 50 MHz) 23.2 (CH$_3$), 28.0 (CH$_3$), 43.4 (NC*C*H$_2$), 50.6 (NCH$_2$), 52.7 (OCH$_3$), 56.7 (NCH), 58.2 (N*C*(CH$_3$)$_2$), 81.6 (C=*C*H$_2$), 99.3 (*C*=C=CH$_2$), 168.3 (C(O)), 171.2 (C(O)), 200.8 (C=*C*=CH$_2$); ms (m/z) 236 ($M^{+\cdot}$), 221, 204, 186, 146, 135, 118, 100; Accurate mass 236.1172 (Calcd for $C_{12}H_{16}N_2O_3$ 236.1161); **20** (light-yellow oil): ir (ν, cm^{-1}, $CHCl_3$) 1730, 1710; ^{1}H nmr (δ, ppm, $CDCl_3$, 200 MHz) 1.24 (s, 6 H, C(CH$_3$)$_2$), 2.61 (s, 2 H, NCCH$_2$), 3.87 (s, 3 H, OCH$_3$), 4.02 (s, 2 H, NCH$_2$), 5.14 (d, *J* = 17.5 Hz, 1 H, =C*H*H), 5.36 (d, *J* = 10.9 Hz, 1 H, =CH*H*), 6.95 (dd, *J* = 10.9, 17.5 Hz, 1 H, *H*C=CH$_2$); ^{13}C nmr (δ, ppm, $CDCl_3$, 50 MHz) 22.5 (C(*C*H$_3$)$_2$, 49.0 + 49.5 (NCH$_2$ + NCCH$_2$), 52.4 (OCH$_3$), 62.7 (N*C*(CH$_3$)$_2$), 127.6 (CH), 119.4, 124.2 + 130.8 (=CH$_2$ + C=C), 159.5 (C(O)), 165.6 (C(O)).

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