TANDEM MICHAEL ADDITION – HOFFMAN ELIMINATION SEQUENCE OF DMAD ON TETRAHYDROPYRROLO[3,2-C]PYRIDINES. NEW ROUTE TO VINYLPYRROLES .

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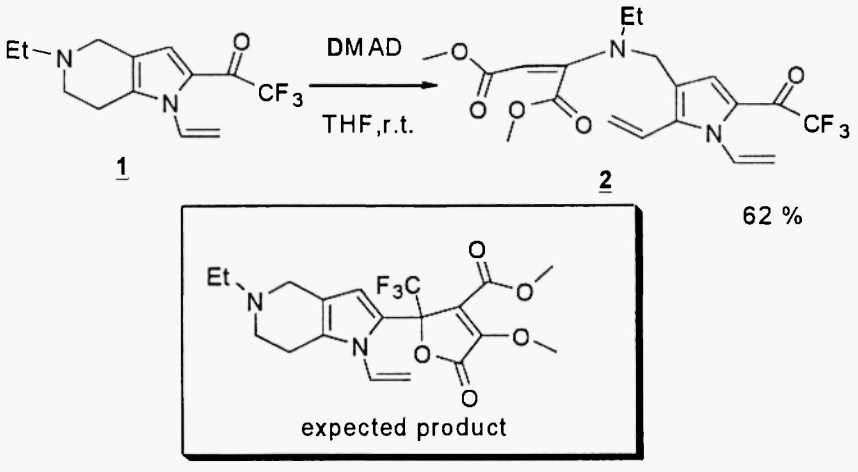
Abstract. The reaction of tetrahydropyrrolo[3,2-c]pyridines with DMAD in THF at room temperature results in piperidine ring cleavage producing α- or β-vinylpyrroles in moderate to good yields. The resulting compounds are hardly available by other synthetic means and are good candidates for further transformations .

Introduction. There are two well-known procedures for piperidine ring cleavage: Hofmann (1) and von Braun (2) reactions . The scope of these reactions is limited and they are most frequently used to determine substituents position in piperidine moiety of natural and synthetic compounds. Recently we have reported piperidine ring cleavage in tetrahydropyrrolo[3,2-c]pyridines under the action of acetic anhydride at 70° C resulting with the formation of 2-(α-methyl-β-acetamidoethyl)-3-vinylpyrroles in moderate yields, while the target 2-acetyl substituted pyrroles have not been isolated (3). In continuation of our studies of pyrrolo[3,2-c]piperidines reactivity and biologic activity investigation (4), we have carried out the reaction of 2-trifluoroacetylsubstituted derivative 1 with DMAD under reflux in THF in the presence of triphenyl phosphine .

Results and Discussion. According to the literature data (5) we expected the formation of a corresponding trifluoromethyl substituted lactone that could exhibit very interesting biologic properties.

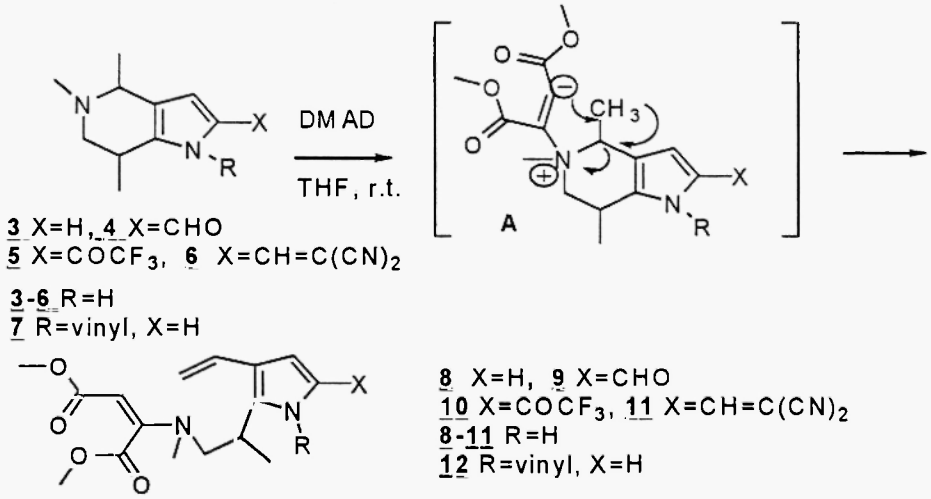
Scheme 1



Surprisingly, the only product obtained (65% yield) was 1,2-divinyl substituted pyrrole 2 , resulting from the piperidine ring cleavage. Compound 2 was later on obtained by the reaction of 1 with DMAD without triphenyl phosphine at room temperature. (Scheme 1).

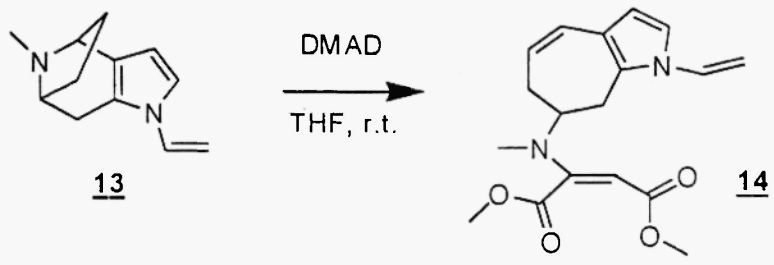
Vinylpyrroles can be used as building blocks for the construction of many natural molecules while the number of synthetic routes to this class of compounds is quite limited. (6) Taking into account this fact and the ready availability of some pyrrolo[3,2-c]piperidines (7) we have studied the reaction of DMAD with 4,5,6,7-tetrahydro-4,5,7-trimethylpyrrolo[3,2-c]pyridine 3 and its 2-substituted derivatives 4-7 under the same reaction conditions. In all cases piperidine ring opening took place and the corresponding 3-vinylpyrrroles 8-12 were isolated in 25-40 % yields (Scheme 2).

Scheme 2



The reaction predictably starts with a nucleophilic attack of piperidine nitrogen atom to the triple bond of DMAD, followed by carbanion A formation . The latter deprotonates β-carbon atom, thus initiating tetrahydropyridine ring cleavage (analogously to the Hofmann reaction). The formation of α- or β-vinylpyrroles from 1 or 3-7 respectively correlates well with this assumption. DMAD also cleaves tropane moiety in N-vinyltetrahydropyrrolo[3,2-c]pyridine 13 giving appropriate cyclohepteno[b]pyrrole 14, similar to those, isolated from the reaction of 13 with acetic or trifluoroacetic anhydrides (3) (Scheme 3).

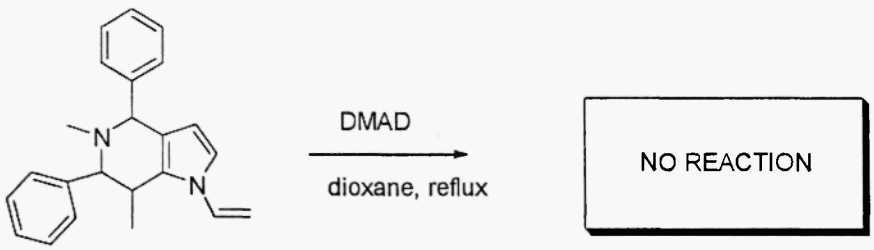
Scheme 3



13 14

The proposed mechanism (Scheme 2) has been indirectly proved by the absence of any reaction (not counting tarring) in the case of diphenyl substituted pyrrolo[3,2-c]piperidine derivative 15 (Scheme 4). Our attempts to cleave the piperidine ring of this compound even under rather forcing conditions (dioxane under reflux, 24 hours) failed. This can be explained by the presence of spatially hindered nitrogen atom, that fails to attack the triple bond of the DMAD molecule.

Scheme 4



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Experimental.

General procedure for 3-vinyl pyrroles synthesis: To a stirred solution of 1 mmol of the corresponding tetrahydropyrrolo[3,2-c]pyridine in 15 ml of dry, freshly distilled THF, solution of 2 mmol of freshly distilled DMAD in 10 ml of THF was added. The reaction mixture was left overnight at room temperature. Evaporation of the solvent under reduced pressure left an oily residue, which was purified by column chromatography on Fluka aluminum oxide (activated, II grade , 150 mesh) (ethyl acetate: heptane, 1:2), affording corresponding vinylpyrroles.

Dimethyl-N-(5-trifluoroacetyl-1,2-divinyl-3-pyrrolyl)methyl-N-ethylamino-2-butene-dioate (2):

Yield: 62%; m.p. 105-106° C; ^{1}H NMR($CDCl_3$): δ 1.13 (t,3H, *J*=7.2, N-CH_2-CH_3). δ 3.17 (q,2H, *J*=7.2, N-CH_2-CH_3), δ 3.64 (s,3H, OCH_3), δ 3.93 (s,3H, OCH_3), δ 4.26 (s, 2H, CH_2-3'), δ 4.68 (s, 1H, H-3), δ 5.22 (dd, 1H, *J*=15.6 ,0.9, H_t-(N-

vinyl)), δ 5.46(dd, 1H, *J*=8.2 ,0.9, H_c-(N-vinyl)), δ 5.48 (dd, 1H, *J*=18.0 ,0.6, H_t-(2'-vinyl)), δ 5.66 (dd, 1H, *J*=11.9 ,0.6, H_c-(2'-vinyl)), δ 6.66 (dd, 1H, *J*=11.9 ,18.0, H_a-(2'-vinyl)), δ 7.20 (q, 1H, ^5J =1.8, H-4'), δ 7.29 (dd, 1H, *J*=8.2, 15.6, H_a-(N-vinyl)); ^{13}C NMR($CDCl_3$) : δ_c 12.3 (CH_2-CH_3), 44.7(CH_2-CH_3), 50.8,52.9 (2 O-CH_3), 51.5(N-CH_2), 85.1(CH-COOMe), 109.5(CH_2-vinyl), 113.1(CH_2-vinyl), 114.7 (CF_3) , 122.1(=C=), 123.3 (HC≡), 124.1 (=C=), 125.6 (HC≡), 131.7(HC≡), 139.2(=C=), 153.8(=C-COOMe), 165.0,165.9 (2 COOMe), 168.0 ($COCF_3$); MS m/z (%) : 414 (10), 395(22), 355(28), 328(50), 228(100), 215(30), 200(40), 158(25), 131(70), 130(90), 104(20), 77(25), 68(31), 59(40), 42(32); HRMS calcd. for $C_{19}H_{21}F_3N_2O_5$:*m/z* 414.1403. Found *m/z* 414.1411.

Dimethyl-N-2-(3-vinyl-1H-2-pyrrolyl)propyl-N-methylamino-2-butene-dioate (8)

Yield 30%, ^{1}H NMR($CDCl_3$): δ 1.24 (d,3H, *J*=7.0, CH-CH_3), δ 2.53 (s,3H, N-CH_3), δ 3.0...3.5 (m,3H,N-CH_2 + CH-CH_3), δ 3.64 (s,3H, OCH_3), δ 3.94 (s,3H, OCH_3), δ 4.53 (s, 1H, H-3), δ 4.97 (dd, 1H, *J*=10.7 ,1.8, H_c-(vinyl)), δ 5.36 (dd, 1H, *J*=17.4 ,1.8, H_t (vinyl)), δ 6.33 (t, 1H, $J_{1',5'}$=, $J_{4',5'}$= 3.1, H-4'), δ 6.62 (dd, 1H, *J*=10.7 ,17.4, H_a-(vinyl)), δ 6.64 (d, 1H, *J*= 3.1, H-5') δ 8.08 (bs, 1H, NH); ^{13}C NMR($CDCl_3$): δ_c 17.4 (CH-CH_3),30.5(CH-CH_3), 38.0(N-CH_3), 50.7,52.9 (2 O-CH_3), 58.8(N-CH_2), 84.7(CH-COOMe), 105.6(CH_2-vinyl), 109.5(CH-4'), 117.5(CH-5'),119.6(C-3') 128.4 (CH-vinyl),130.1 (C-2'), 154.5(=C-COOMe), 166.3,167.9 (2 COOMe); MS m/z (%) : 306 (15), 275 (18), 247 (40), 235 (12), 212 (22), 186 (100), 120 (80), 107 (40), 91(15), 82 (52), 45(25); HRMS Calcd for $C_{16}H_{22}N_2O_4$. *m/z* 306.1580. Found *m/z* 306.1584.

Dimethyl-N-2-(5-formyl-3-vinyl-1H-2-pyrrolyl)propyl-N-methylamino-2-butene-dioate (9)

Yield 26%; m.p. 110-112 °C; ^{1}H NMR($CDCl_3$): δ 1.33 (d,3H, *J*=6.7, CH-CH_3), δ 2.60 (s,3H, N-CH_3), δ 3.42 (m,1H, N-CH_2), 3.47...3.49 (m,2H, CH-CH_3 +N-CH_2), δ 3.65 (s,3H, OCH_3), δ 3.93 (s,3H, OCH_3), δ 4.60 (s, 1H, H-3), δ 5.14 (dd, 1H, *J*=10.1 ,1.1, H_c-(vinyl)), δ 5.52(dd, 1H, *J*=16.3 ,1.1, H_t (vinyl)), δ 6.59 (dd, 1H, *J*=10.1 ,16.3, H_a-(vinyl)), δ 7.11 (s, 1H, H-4'), δ 9.45 (s, 1H, CHO), δ 10.04 (bs, 1H, NH); ^{13}C NMR($CDCl_3$): δ_c 16.8 (CH-CH_3),31.0(CH-CH_3), 38.5(N-CH_3), 50.7,52.9 (2 O-CH_3), 58.4(N-CH_2), 85.1(CH-COOMe), 112.5(CH_2-vinyl), 118.7(CH-4'), 123.1 (C-3'), 126.9 (CH-vinyl),132.0 (C-5'), 140.8 (C-2'), 154.3(=C-COOMe), 165.9,167.9 (2 COOMe), 179.0 (CHO); MS m/z (%) : 334 (2), 187 (8), 186 (100), 118 (5) 91(6), 82 (23), 45 (8); HRMS Calcd for $C_{17}H_{22}N_2O_5$ 334.1529, found *m/z* 334.1531

Dimethyl-N-2-(5-trifluoroacetyl-3-vinyl-1H-2-pyrrolyl)propyl-N-methylamino-2-butene-dioate (10)

Yield 32%; ^{1}H NMR($CDCl_3$): δ 1.33 (d,3H, *J*=7.0, CH-CH_3), δ 2.60 (s,3H, N-CH_3), δ 3.20...3.60 (m,3H, N-CH_2+ CH-CH_3), δ 3.64 (s,3H, OCH_3), δ 3.92 (s,3H, OCH_3), δ 4.56 (s, 1H, H-3), δ 5.21 (dd, 1H, *J*=11.0 ,1.2, H_c-(vinyl)), δ 5.55 (dd, 1H, *J*=17.4 ,1.2, H_t (vinyl)), δ 6.57 (dd, 1H, *J*=11.0, 17.4, H_a-(vinyl)), δ 7.29 (m, 1H, H-4'), δ 9.84 (bs, 1H, NH); ^{13}C NMR($CDCl_3$): δ_c 16.6 (CH-CH_3),31.5(CH-CH_3), 38.7(N-CH_3), 50.7,53.0 (2 O-CH_3), 58.3(N-CH_2), 85.5(CH-COOMe), 114.2(CH_2-vinyl), 117.0 (CF_3) , 118.7(CH-4'), 124.7 (C-5'), 124.9 (C-3'), 126.2 (CH-vinyl),144.1 (C-2'), 154.1(=C-COOMe), 165.9,167.8 (2 COOMe), 169.6 ($COCF_3$); MS m/z (%) : 402 (3), 371 (8), 187(13), 186 (100), 82 (34), 45 (11); HRMS Calcd for $C_{18}H_{21}F_3N_2O_5$ 402.1403, found *m/z* 402.1406

Dimethyl- N-2-[5-(2,2-Dicyanovinyl)-3-vinyl-1H-2-pyrrolyl]propyl-N-methylamino-2-butene-dioate (11)

Yield 41%; m.p. 92-94°C; ^{1}H NMR($CDCl_3$): δ 1.30 (d,3H, *J*=7.2, CH-C<u>H</u>$_3$), δ 2.65 (s,3H, N-C<u>H</u>$_3$), δ 3.20...3.60 (m,3H, N-C<u>H</u>$_2$+ C<u>H</u>-CH$_3$), δ 3.68 (s,3H, OC<u>H</u>$_3$), δ 3.97 (s,3H, OC<u>H</u>$_3$), δ 4.60 (s, 1H, H-3), δ 5.21 (dd, 1H, *J*=10.9, 1.3, H_c-(vinyl)), δ 5.60 (dd, 1H, *J*=17.0 ,1.2, H_t (vinyl)), δ 6.55 (dd, 1H, *J*=10.9, 17.0, H_a-(vinyl)), δ 7.26 (s, 1H, H-4'), δ 7.45 (s,1H, CH-5'-vinyl), δ 9.84 (bs, 1H, NH); MS m/z (%) : 382(8), 351(7), 323(7), 200(15), 186 (100), 140(6), 82(19), 45(12); CHN % analysis: Calcd for $C_{20}H_{22}N_4O_4$:C 62.82%, H 5.80% ,N 14.65% Found C 62.54%, H 5.53% ,N 14.82%

Dimethyl-N-2-(1,3-divinyl-2-pyrrolyl)propyl-N-methylamino-2-butene-dioate (12)

Yield 47%; ^{1}H NMR($CDCl_3$): δ 1.32 (d,3H, *J*=6.7, CH-C<u>H</u>$_3$), δ 2.48 (s,3H, N-C<u>H</u>$_3$), δ 3.2...3.5 (m,3H, N-C<u>H</u>$_2$+ C<u>H</u>-CH$_3$), δ 3.64 (s,3H, OC<u>H</u>$_3$), δ 3.93 (s,3H, OC<u>H</u>$_3$), δ 4.52 (s, 1H, H-3), δ 4.76 (dd, 1H, *J*=8.9 ,0.9, H_c-(N-vinyl)), δ 5.01 (dd, 1H, *J*=10.7 ,1.8, H_c-(3'-vinyl)), δ 5.10 (dd, 1H, *J*=15.6 ,0.9, H_t-(N-vinyl)), δ 5.37 (dd, 1H, *J*=17.4 ,1.8, H_t-(3'-vinyl)), δ 6.37(d, 1H, *J*=3.4, H-4'), δ 6.69 (dd, 1H, *J*=10.7 ,17.4, H_a-(3'-vinyl)), δ 6.88 (d, 1H, *J* =3.4, H-5'), δ 6.92 (dd, 1H, *J*=8.9, 15.6, H_a-(N-vinyl)); ^{13}C NMR($CDCl_3$): δ_c 17.6 (CH-<u>C</u>H$_3$),31.0(<u>C</u>H-CH$_3$), 38.2(N-<u>C</u>H$_3$), 51.4,52.8 (2 O-<u>C</u>H$_3$), 58.4(N-<u>C</u>H$_2$), 84.6(<u>C</u>H-COOMe), 100.9(<u>C</u>H$_2$-vinyl-1'), 107.1 (<u>C</u>H-4'),110.7(<u>C</u>H$_2$-vinyl-3'), 117.9 (<u>C</u>H-5'), 121.6 (<u>C</u>-3'), 128.4 (<u>C</u>H-vinyl-3'), 130.1 (<u>C</u>-2'), 130.6 (<u>C</u>H-vinyl-1'), 154.4(=<u>C</u>-COOMe), 165.9,167.9 (2 <u>C</u>OOMe)); MS m/z (%) 332 (7), 212 (10), 186 (100), 146 (56), 144 (12), 133 (23), 132 (20), 131 (13), 130 (15), 118 (12), 91 (10), 82 (63), 59 (14), 45 (50), 43 (13), 42 (17), 41 (12); HRMS Calcd for $C_{18}H_{24}N_2O_4$ *m/z* 332.1736 , found *m/z* 332.1731

Dimethyl -N-(1-vinyl-1,6,7,8-tetrahydro-cyclohepta[b]pyrrol-7-yl)-N-methylamino-but-2-ene-dioate (14)

Yield 35%;^{1}H NMR($CDCl_3$): δ 2.35...2.75 (m, 2H, CH_2-6'), δ 2.78 (s,3H, N-CH_3), δ 2.9...3.2 (m, 2H, CH_2-8'), δ 3.63 (s,3H, OC<u>H</u>$_3$), δ 3.65...3.80 (m, 1H, H-7'), δ 3.87 (s,3H, OC<u>H</u>$_3$), δ 4.66 (s, 1H, H-3), δ 4.74 (dd, 1H, *J*=8.5 ,1.2, H_c-(N-vinyl)), δ 5.11 (dd, 1H, *J*=15.6 ,1.2, H_t-(N-vinyl)), δ 5.53 (m, 1H, H-5'), δ 6.05 (d, 1H, *J*=3.1, H-3'), δ 6.21 (dd, *J*=11.3 ,2.8, H-4'), δ 6.79 (dd, 1H, *J*=8.5, 15.6, H_a-(N-vinyl)), δ 6.91 (d, 1H, *J*=3.1, H-2'); δ_c 31.3 (N-<u>C</u>H$_3$), 32(<u>C</u>H$_2$), 34.4(<u>C</u>H$_2$), 50.7,52.9 (2 O-<u>C</u>H$_3$), 57.0 (<u>C</u>H-7'), 84.5(<u>C</u>H-COOMe), 99.8(<u>C</u>H$_2$-vinyl-1'), 111.1(<u>C</u>H-3'), 116.5(<u>C</u>H-2'),120.0 (<u>C</u>-3''),120.8(*C*H-5'),124.4(*C*-8''), 124.8(*C*H-4'), 129.9(*C*H-vinyl),154.3(=*C*-COOMe), 165.9,168.0 (2 *C*OOMe); MS m/z (%):330 (26), 232 (11), 231 (70), 210 (10), 172 (11), 158 (38), 157 (100), 156 (65), 144 (20), 143 (17), 142 (15), 132 (9), 131 (18), 130 (27), 129 (11), 128 (13), 117 (19), 116 (11), 115 (30), 105 (11), 103 (15), 91 (29), 82 (27), 78 (11), 77 (24), 59 (22), 56 (14), 55 (19), 54 (17); HRMS Calcd for $C_{18}H_{22}N_2O_4$ *m/z* 330.1580 , found *m/z* 330.1577

Conclusions. We have demonstrated the possibility of piperidine ring cleavage in tetrahydropyrrolo[3,2-c]pyridines under the action of DMAD. The availability of the starting material and mild reaction conditions make this reaction very attractive and stimulate further work aimed at optimisation of the experimental procedure as well as at the reaction scope and limitations determination .

References and Notes.

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