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NOVEL PREPARATIVE METHOD FOR SYNTHESIS OF ISOINDOLO[2,1-*b*]BENZ-2-AZEPINE-8-CARBOXYLIC ACIDS

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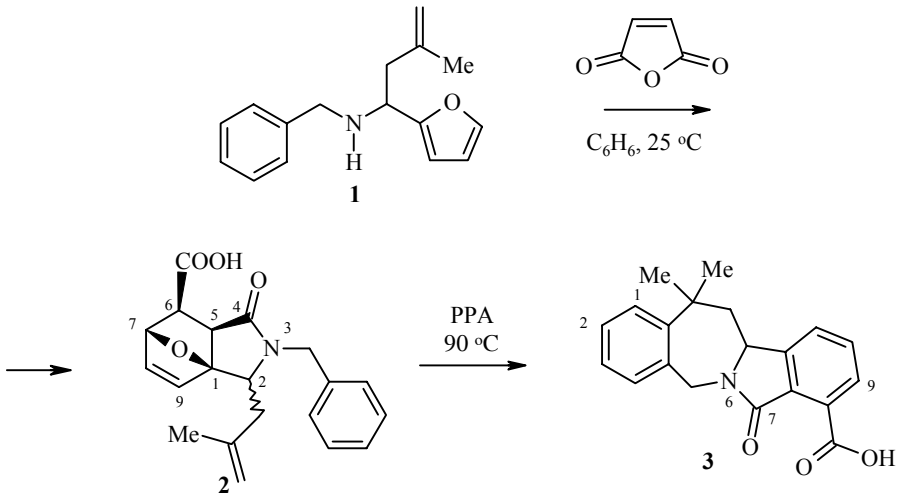
Based on readily accessible homoallyl amines, we previously developed preparative methods for synthesis of substituted and spiro-annelated tetrahydroquinolines [1], 3-aza-11-oxatricyclo[6.2.1.01,6]undec-9-enes (6,8a-epoxy isoquinolines) [2], γ-piperidoles [3], benz-2-azepines [4], isoindolo[2,1-*a*]quinoline-10-carboxylic acids [5].

In continuing our work on studying the synthetic possibilities for furyl-substituted homoallyl amines, we carried out an original two-step synthesis for isoindolo[2,1-*b*]benz-2-azepine **3**.



By [4+2] cycloaddition of maleic anhydride to homoallyl amine **1**, obtained by reaction of N-furfurylidenebenzylamine and methallylmagnesium chloride [3], epoxy isoindolone **2** was synthesized in quantitative yield [6]. The intramolecular Diels–Alder reaction occurs stereospecifically to form the *exo* adduct **2**, which is a mixture of two geometric isomers (~1:1) with respect to the position of the epoxide bridge and the methallyl substituent. Simultaneous aromatization of the 7-oxabicyclo[2.2.1]heptene moiety and electrophilic intramolecular cyclization of the methallyl radical of compound **2** when treated with PPA [polyphosphoric acid] lead to azepine **3**.

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In contrast to existing unwieldy methods for synthesis of isoindolo-[2,1-*b*]benz-2-azepines [7-10], our method is distinguished by the simplicity of the experiment and the accessibility of the starting compounds.

3-Benzyl-2-methallyl-4-oxo-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic Acid (2). A mixture of maleic anhydride (43.4 g, 443 mmol) and freshly distilled 4-(N-benzylamino)-2-methyl-4-(2-furyl)-1-butene (**1**) (106.8 g, 443 mmol) in toluene (500 ml) was stirred for 40 h at 25°C. The precipitated crystals were filtered out and washed successively with toluene (100 ml) and ether (2 × 150 ml), and then dried for 2 h at 100°C until the mass remained constant. Obtained 140.9 g of a mixture of isomers (~1:1) of adduct **2**, white crystals; mp 169-170°C. Yield 94%. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): isomer **A** – 11.03 (1H, br. s, COOH); 7.45-7.15 (5H, m, H-Ph); 6.48 (1H, d, $J_{9,8}$ = 5.8, 9-H); 6.35 (1H, dd, $J_{8,9}$ = 5.8, $J_{7,8}$ = 1.5, 8-H); 5.25 (1H, d, $J_{7,8}$ = 1.5, 7-H); 5.09 (1H, d, J_{AB} = 15.0, C$\underline{H}_A$H$_B$Ph); 4.92 (1H, br. s, 1'-H); 4.82 (1H, br. s, 1'-H); 4.08 (1H, d, J_{AB} = 15.0, CH$_A\underline{H}_B$Ph); 3.95 (1H, dd, $J_{2,3'A}$ = 8.2, $J_{2,3'B}$ = 5.5, 2-H); 3.04 (1H, d, $J_{5,6}$ = 9.2, 5-H); 2.83 (1H, d, $J_{5,6}$ = 9.2, 6-H); 2.55-2.40 (2H, m, 3'A-H and 3'B-H); 1.71 (3H, s, 2'-Me); isomer **B** – 11.03 (1H, br. s, COOH); 7.45-7.15 (5H, m, H-Ph); 6.28 (2H, s, 9-H and 8-H); 5.29 (1H, s, 7-H); 4.95 (1H, d, J_{AB} = 15.0, C$\underline{H}_A$H$_B$Ph); 4.82 (1H, br. s, 1'-H); 4.71 (1H, br. s, 1'-H); 4.19 (1H, d, J_{AB} = 15.0, CH$_A\underline{H}_B$); 4.10 (1H, dd, $J_{2,3'A}$ = 8.1, $J_{2,3'B}$ = 6.6, 2-H); 2.89 (1H, d, $J_{5,6}$ = 9.2, 5-H); 2.83 (1H, d, $J_{5,6}$ = 9.2, 6-H); 2.55-2.40 (2H, m, 3'A-H and 3'B-H); 1.59 (3H, s, 2'-CH_3). IR spectrum (KBr), ν, cm^{-1}: 1640 (COOH), 1710 (N–C=O). Mass spectrum, *m*/*z* (I_{rel}, %): [M]$^+$ 339 (2), 284 (10), 266 (1), 240 (2), 218 (1), 204 (8), 194 (7), 150 (2), 134 (3), 120 (6), 99 (12), 91 (100), 78 (16), 71 (4), 65 (16), 51 (8), 39 (10). Found, %: C 74.80; H 6.21; N 4.10. $C_{20}H_{21}NO_4$. Calculated, %: C 70.80; H 6.20; N 4.13.

13,13-Dimethyl-7-oxo-5,6,7,11b,12,13-hexahydroisoindolo[2,1-*b*]benz-2-azepine-8-carboxylic Acid (3). PPA (380 ml) (prepared from 200 g of P_2O_5 and 200 ml of 85% H_3PO_4) was added quickly with rapid stirring to finely ground epoxy isoindolinone **2** (60.0 g, 177 mmol). The mixture was heated for 40 min at 90°C (homogenization was observed), cooled down to 70°C, and poured into water (400 ml). The precipitating crystals were filtered out, washed with ice water (3 × 300 ml) and isopropyl alcohol (2 × 150 ml), dried in air until the weight remained constant, and recrystallized from an *i*-PrOH–DMF mixture. Obtained 38.4 g (120 mmol) of acid **3** as lustrous white needles; mp 255-257°C. Yield: 67%. ^{1}H NMR spectrum (400 MHz, DMSO), δ, ppm (*J*, Hz): 9.03 (1H, br. s, COOH); 8.12 (1H, dd, $J_{9,10}$ = 7.7, $J_{9,11}$ = 0.7, 9-H); 7.99 (1H, br. d, $J_{11,10}$ = 7.7, 11-H); 7.82 (1H, t, $J_{11,10}$ = $J_{9,10}$ = 7.7, 10-H); 7.41 (1H, dd, *J* = 1.1 and 7.5, 4-H); 7.37 (1H, dt, *J* = 1.6 and 7.5, 2-H); 7.37 (1H, dt, *J* = 1.1 and 7.5, 3-H); 7.21 (1H, dd, *J* = 1.6 and 7.5, 1-H); 5.30 (1H, dd, $J_{12A,11b}$ = 3.4, $J_{12B,11b}$ = 11.9, 11b-H); 5.13 (1H, d, $J_{5A,5B}$ = 15.5, 5A-H); 4.97 (1H, d, $J_{5A,5B}$ = 15.5, 5A-H); 2.55 (1H, dd, $J_{12A,11b}$ = 3.4, $J_{12A,12B}$ = 14.0, 12A-H); 1.57 (3H, s, 13-CH_3); 1.47 (3H, s, 13-CH_3); 1.42 (1H, dd, $J_{12B,11b}$ = 11.9, $J_{12A,12B}$ = 14.0, 12B-H). IR spectrum (KBr), ν, cm^{-1}: 1680 (N–C=O), 1700 (COOH). Mass spectrum, *m*/*z* (I_{rel}, %): [M]$^+$ 321 (27), 320 (3), 306 (2), 304 (2), 304 (2), 279 (2), 278 (13), 277 (52), 276 (20), 275 (100), 262 (1), 234 (2), 220 (2), 202 (2), 193 (2), 165 (2), 145 (3), 131 (14), 115 (8), 103 (3), 91 (14), 77 (3), 65 (1), 28 (2). Found, %: C 74.78; H 5.90; N 4.37. $C_{20}H_{19}NO_3$. Calculated, %: C 74.75; H 5.96; N 4.36.

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REFERENCES

1. V. V. Kouznetsov, A. R. Palma, A. V. Varlamov, *J. Heterocycl. Chem.*, **35**, 761 (1998).
2. A. V. Varlamov, E. V. Nikitina, F. I. Zubkov, O. V. Shyrupova, and A. I. Chernyshev, *Mendeleev Commun.*, **12**, 32 (2002).
3. A. Varlamov, V. Kouznetsov, F. Zubkov, A. Chernyshev, O. Shurupova, L. Y. Vargas Mendez, A. Palma, J. Rivero Castro, and A. J. Rosas-Romero, *Synthesis*, 771 (2002).

4. A. Varlamov, V. Kouznetsov, F. Zubkov, A. Chernyshev, G. Alexandrov, A. Palma, L. Vargas, and S. Salas, *Synthesis*, 849 (2001).
5. A. V. Varlamov, F. I. Zubkov, E. V. Boltukhina, N. V. Sidorenko, and R. S. Borisov, *Tetrahedron Lett.*, **44**, 3641 (2003).
6. E. V. Nikitina, A. A. Safronova, A. V. Varlamov, F. I. Zubkov, G. G. Aleksandrov, and K. F. Turchin, *Khim. Geterotsikl. Soedin.*, 138 (2003).
7. R. Faust, P. J. Garratt, R. Jones, and L.-K. Yeh, *J. Med. Chem.*, **43**, 1050 (2000).
8. A. Daïch, S. Marchalin, P. Pigeon, and B. Decroix, *Tetrahedron Lett.*, **39**, 9187 (1998).
9. Y. Ishihara, T. Tanaka, S. Miwatashi, A. Fujishima, and G. Goto, *J. Chem. Soc., Perkin Trans. I*, 2993 (1994).
10. Y. Ishihara, Y. Kiyota, and G. Goto, *Chem. Pharm. Bull.*, **38**, 3024 (1990).