Chemistry of Heterocyclic Compounds, Vol. 45, No. 3, 2009

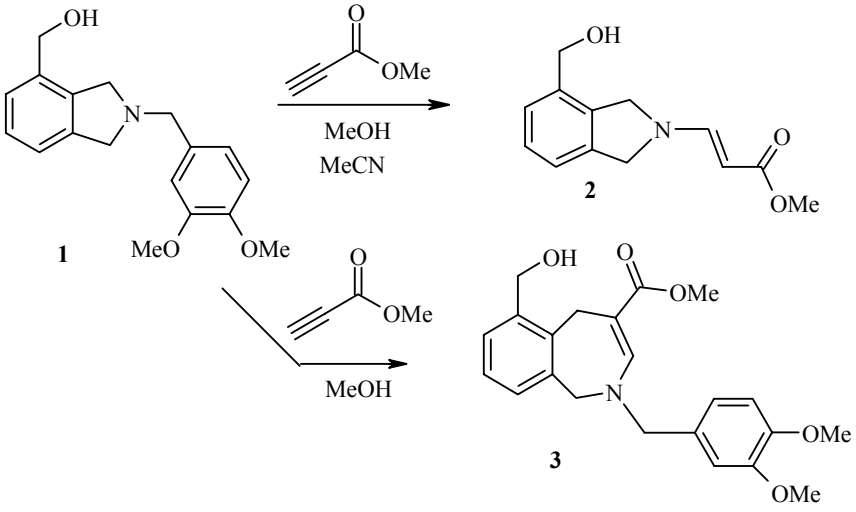
INTERACTION OF 4-HYDROXYMETHYL-2-(3,4-DIMETHOXYBENZYL)ISOINDOLINE WITH METHYL PROPIOLATE

L. G. Voskressensky[1]*, L. N. Kulikova[1], A. V. Kleimenov[1], T. N. Borisova[1], E. V. Nikitina[1], A. V. Listratova[1], and A. V. Varlamov[1]

Keywords: benzo[*c*]azepine, isoindoline.

We showed previously that tetrahydropyrrolopyridines and hexahydroazepinoindoles, under the action of alkynes activated by electron-withdrawing substituents, undergo, depending on the type of solvent, either expansion of the hydrogenated aza fragment, or its decomposition. In this way tetrahydropyrroloazocines and hexahydroazoninoindoles or substituted pyrroles and indoles [1, 2] respectively are formed. This reaction is an efficient method of synthesizing condensed azocines and azonines.

Transformation of isoindolines by alkynes have not previously been studied. We synthesized 2-dimethoxybenzyl-4-hydroxymethylisoindoline (**1**) by the reduction of 2-dimethoxybenzyl-3-oxoisoindoline-4-carboxylic acid [3] with lithium aluminum hydride and studied its conversion under the action of methyl propiolate in acetonitrile and methanol at 20 and -10°C.



* To whom correspondence should be addressed, e-mail: lvoskressensky@sci.pfu.edu.ru.

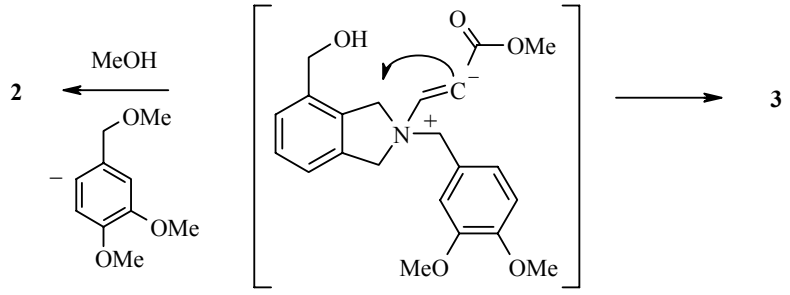
[1]Russian Peoples' Friendship University, Moscow 117198, Russia.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 456-458, March, 2009. Original article submitted March 12, 2009.

 0009-3122/09/4503-0372©2009 Springer Science+Business Media, Inc.

Debenzylation of compound **1** occurs in methanol and acetonitrile at 20°C with the formation of methoxycarbonylvinyl-substituted derivative **2**. At a temperature from -5 to -10°C the competing processes of debenzylation and expansion of the isoindoline fragment leads to a mixture of isoindoline **2** and benzoazepine **3**.

The observed conversions of isoindoline **1** under the action of methyl propiolate occur through the formation of a zwitterion.



A

The high capability of the dimethoxybenzyl radical towards cationic fission causes the formation of the debenzylation product **2**. Nucleophilic attack of the anionic center of **A** at position 3 leads to the ring expansion product azepine **3**. It is possible that the formation of compound **3** at low temperature is caused by the fact that the energy of activation of the expansion process is less than that of debenzylation.

The possibility has therefore been shown for the first time of expanding the tetrahydropyrroline ring to an azepine under the action of activated alkynes.

The ^{1}H NMR spectra were obtained on a Jeol JNM-ECA 600 instrument (600 MHz) in $CDCl_3$, internal standard was TMS.

[2-(3,4-Dimethoxybenzyl)-2,3-dihydro-1H-isoindol-4-yl]methanol (1). 2-(3,4-Dimethoxybenzyl)-3-oxoindoline-4-carboxylic acid (5 g, 15.3 mmol) was added in portions to a suspension of lithium aluminum hydride (2.32 g, 62 mmol) in dioxane (100 ml) and the mixture was boiled. A check on the progress of the reaction was effected by TLC. The reaction mixture was cooled to 20°C and decomposed by adding sequentially, dropwise, ethyl acetate (30 ml) and a 5% sodium hydroxide solution (100 ml), and the mixture was extracted with ethyl acetate (3×100 ml). The extract was dried over sodium sulfate. After distillation of the ethyl acetate in vacuum the residue was crystallized from a mixture of hexane and ethyl acetate. Isoindole **1** (3.14 g, 70%) of mp 134°C was obtained. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.73 (2H, s, NCH_2); 3.79 (3H, s, OCH_3); 3.85 (3H, s, OCH_3); 3.82 (2H, s, NCH_2); 4.77 (2H, s, $C\underline{H}_2OH$); 6.78-7.32 (6H, m, arom.). Found, %: C 72.22; H 7.07; N 4.68. M^+ 299. $C_{18}H_{21}NO_3$. Calculated, %: C 72.28; H 7.04; N 4.70.

Interaction of Isoindoline 1 with Methyl Propiolate. A solution of isoindoline **1** (0.51 g, 1.7 mmol) and methyl propiolate (0.2 g, 2.5 mmol) in methanol or acetonitrile (10 ml) was maintained at 20°C or -5°C until the disappearance of the starting material (check on the progress of the reaction by TLC). The solvent was evaporated in vacuum, and the residue obtained was chromatographed on silica gel, eluent was ethyl acetate–hexane, 1:20 to 1:1. Compounds **2** and **3** were obtained.

2-(3,4-Dimethoxybenzyl)-6-(hydroxymethyl)-2,5-dihydro-1H-2-benzoazepine-4-carboxylic Acid Methyl Ester (3). Yield was 40%, white crystals of mp 129°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.69 (3H, s, CO_2CH_3); 3.84 (3H, s, OCH_3); 3.87 (3H, s, OCH_3); 3.89 (2H, s, NCH_2); 4.61 (2H, d, J = 4.6, $C\underline{H}_2OH$); 4.85 (2H, s, NCH_2); 4.91 (2H, s, NCH_2); 6.78 (3H, m, arom.); 7.09-7.32 (3H, m, arom.); 7.87 (1H, s, H-3). Found, %: C 68.74; H 6.41; N 3.71. M^+ 383. $C_{22}H_{25}NO_5$. Calculated, %: C 68.91; H 6.57; N 3.65.

3-[4-(Hydroxy)-1,3-dihydro-2H-isoindolyl]acrylic Acid Methyl Ester (2). Yield was 19%, yellowish crystals, mp 116°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.67 (3H, s, CO_2CH_3); 3.82 (2H, s, NCH_2); 3.84 (2H, s, NCH_2); 4.65 (1H, d, J = 13.1, $=CHCO_2CH_3$); 4.9 (2H, s, $C\underline{H}_2OH$); 7.19-7.34 (3H, m, arom.); 7.73 (1H, d, J = 13.1, NCH=). Found, %: C 66.71; H 6.63; N 6.12. M^+ 233. $C_{13}H_{15}NO_3$. Calculated, %: C 66.95; H 6.44; N 6.00.

The work was carried out with the financial support of the Russian Fund for Fundamental Investigations (RFFI) (grant No. 08-03-90451 Ukr-a).

REFERENCES

1. L. G. Voskresensky, T. N. Borisova, T. A. Vorob′eva, A. I. Chernyshev, and A. V. Varlamov, *Izv. Akad. Nauk, Ser. Khim.*, 2513 (2005).
2. L. G. Voskressensky, S. V. Akbulatov, T. N. Borisova, and A. V. Varlamov, *Tetrahedron*, **62**, 12392 (2006).
3. F. I. Zubkov, E. V. Boltukhina, K. E. Turdin, R. S. Borisov, and A. V. Varlamov, *Tetrahedron*, **61**, 4009 (2005).