ISSN 1070-4280, Russian Journal of Organic Chemistry, 2008, Vol. 44, No. 12, pp. 1831–1835. © Pleiades Publishing, Ltd., 2008.
Original Russian Text © A.M. Atnabaeva, Z.S. Muslimov, R.I. Khusnutdinov, U.M. Dzhemilev, 2008, published in Zhurnal Organicheskoi Khimii, 2008, Vol. 44, No. 12, pp. 1858–1861.

Synthesis of 2-Ethyl-3,5-dimethylpyridine by Heterocyclization of Allylamine, Cyclopropylamine, and Diallylamine in the Presence of Palladium Complexes

A. M. Atnabaeva, Z. S. Muslimov, R. I. Khusnutdinov, and U. M. Dzhemilev

Institute of Petroleum Chemistry and Catalysis, Russian Academy of Sciences,
pr. Oktyabrya 141, Ufa, 450075 Bashkortostan, Russia
e-mail: ink@anrb.ru

Received March 27, 2008

Abstract—2-Ethyl-3,5-dimethylpyridine was synthesized by disproportionation and heterocyclization of allylamine, cyclopropylamine, and diallylamine in the presence of palladium catalysts.

DOI: 10.1134/S1070428008120208

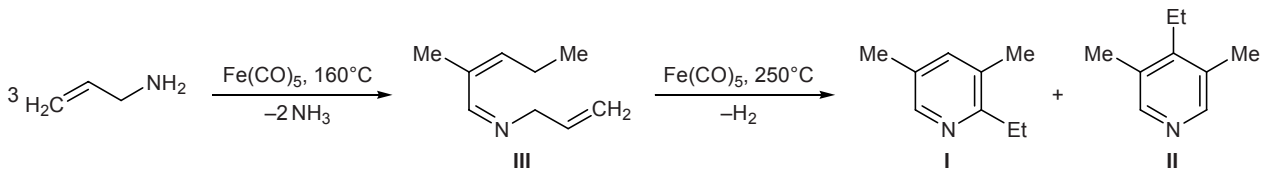
2-Ethyl-3,5-dimethylpyridine (**I**) is used in the synthesis of corrosion inhibitors and drugs [1, 2]. In particular, demethylenation of **I** gives 2,3,5-trimethylpyridine as starting material for the preparation of up-to-date highly effective antiulcer drug Omeprazole [2]. A classical procedure for the synthesis of 2-ethyl-3,5-dimethylpyridine (**I**) is based on the condensation of propionaldehyde with ammonia over $Co_3(PO_4)_2$ at 350–420°C [3]. As a result, a mixture of three pyridine bases is formed: 2-ethyl-3,5-dimethylpyridine (**I**), 4-ethyl-3,5-dimethylpyridine (**II**), and 3,4-dimethylpyridine. Compound **I** was obtained in 17% yield by reaction of *N*-propylidenepropenamine with propylene over heterogeneous catalyst K_2O/Al_2O_3 at 410–415°C [4]; the reaction was accompanied by formation of 2-ethyl-4,5-dimethylpyridine.

2-Ethyl-3,5-dimethylpyridine (**I**) can be obtained with a higher yield (~30%) by heterocyclization of *N*-propenylprop-2-en-1-amine in the presence of Ni/Al_2O_3 [5]. Falbe et al. [6] described an unusual procedure for the synthesis of 2-ethyl-3,5-dimethylpyridine (**I**) from allylamine by the action of (pentacarbonyl)iron $Fe(CO)_5$ (Scheme 1). The reaction includes several steps. Initially, allylamine under relatively mild conditions (160°C) undergoes disproportionation with elimination of ammonia, the subsequent Cope rearrangement gives *N*-(2-methylpent-2-en-1-ylidene)prop-2-en-1-amine (**III**), and heterocyclization of the latter at higher temperature (250°C), followed by dehydrogenation, leads to a mixture of 2-ethyl-3,5-dimethylpyridine (**I**) as the major product and 4-ethyl-3,5-dimethylpyridine (**II**) in an overall yield of 30%. The authors succeeded in isolating intermediate azatriene **III** and characterizing it by spectral methods.

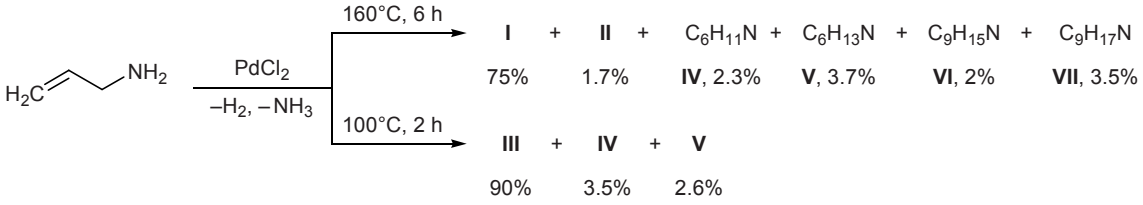
Taking into account accessibility of allylamine and simplicity of the experimental procedure, we set ourselves the goal of studying heterocyclization of allylamine, its structural analog cyclopropylamine, and diallylamine in the presence of palladium complexes. The latter were selected as catalysts taking into account that palladium compounds are capable of promoting not only dehydrogenation but also double bond migration [7] and aza-Cope rearrangement [8, 9].

In the presence of 1 mol % of $PdCl_2$ at 160°C allylamine was selectively converted into compound **I** in 69% yield in 6 h (Scheme 2). According to the GC–MS data, the reaction mixture contained alkylpyridines **I** and **II** and products resulting from isomerization and

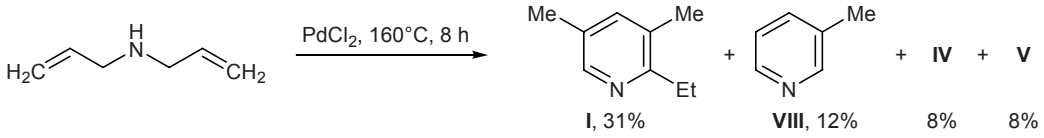
Scheme 1.



Scheme 2.



Scheme 3.



partial hydrogenation of diallylamine (**IV**, *m*/*z* 97; **V**, *m*/*z* 99) and triallylamine (**VI**, *m*/*z* 137; **VII**, *m*/*z* 139). Compound **VI** was a mixture of five isomeric tris(prop-1-en-1-yl)amines differing by configuration of the double bonds [10]. The reaction performed at 100°C gave azatriene **III** in 90% yield, the conversion of allylamine being 100%.

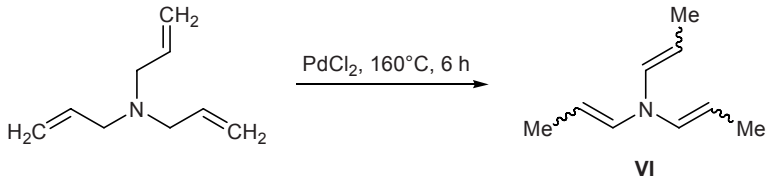
When azatriene **III** isolated by vacuum distillation was heated for 4 h at 160°C in the presence of 1 mol % of $PdCl_2$, 2-ethyl-3,5-dimethylpyridine (**I**) was obtained in almost quantitative yield. Analogous reaction at lower temperature (130°C) gave compounds **I** and **VI** at a ratio of 1:1.2.

Comparison of the analytical data for 2-ethyl-3,5-dimethylpyridine (**I**, $C_9H_{13}N$) and intermediate azatriene **III** ($C_9H_{15}N$) suggests that compound **I** is formed in several steps, including disproportionation, double bond isomerization, cyclization, and dehydrogenation. Assuming that diallylamine is formed as intermediate in the transformation of **III** into **I**, we examined the behavior of diallylamine under the above conditions. In fact, diallylamine underwent heterocyclization to produce pyridine **I**, but the selectivity of this process was lower than in the reaction with allylamine. The complete conversion of diallylamine was reached in 8 h at 160°C, and the reaction mixture contained 31% of compound **I**, 12% of 3-methylpyridine (**VIII**), 8% of **IV** and **V** each, and ~40% of higher oligomers (Scheme 3). Unlike diallylamine, triallylamine did not undergo heterocyclization in the presence of $PdCl_2$; instead, a mixture of *Z* and *E* isomers of tris(prop-1-en-1-yl)amine (**VI**) was formed, the substrate conversion being almost complete (Scheme 4).

Replacement of $PdCl_2$ by K_2PdCl_4 resulted in reduced selectivity for 2-ethyl-3,5-dimethylpyridine (**I**, 18%), while 22% of 3-methylpyridine (**VIII**) and 10% of *N*,*N*-diallylpropan-1-amine (**VII**) were formed as by-products. The reaction catalyzed by $Pd(acac)_2$ gave 36% of **I** and an appreciable amount (12%) of 4-ethyl-3,5-dimethylpyridine (**II**) (Scheme 5).

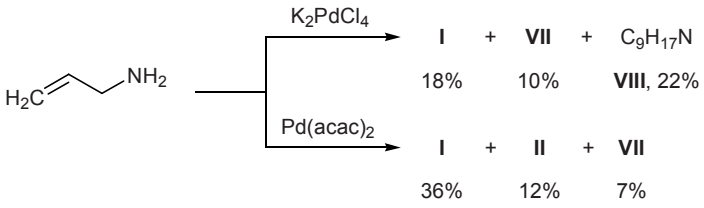
The formation of partially hydrogenated product **VII** from triallylamine may be rationalized taking into

Scheme 4.



VI

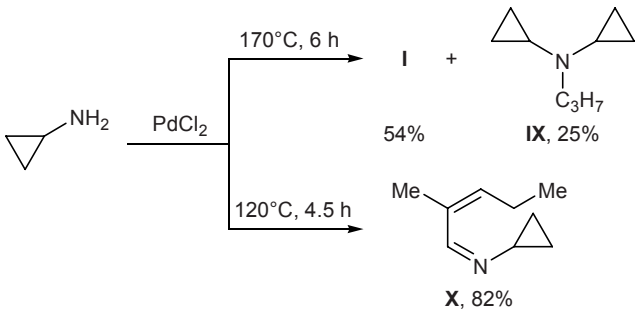
Scheme 5.



account, on the one hand, liberation of hydrogen and, on the other, well-known ability of palladium complexes to catalyze hydrogenation processes. Our attempt to suppress side hydrogenation of intermediate unsaturated amines by adding norbornene (which is known to readily undergo hydrogenation under mild conditions) to the reactions mixture was unsuccessful.

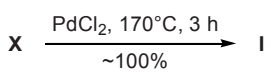
According to published data, cyclopropylamine (which is isomeric to allylamine) can be converted into allylamine (cyclopropyl–allyl rearrangement) in the presence of palladium complexes [11]. Therefore, we anticipated that heterocyclization of cyclopropylamine would give rise to alkyl-substituted pyridines. The results of our experiments confirmed the above assumption. When cyclopropylamine was heated for 6 h at 170°C in the presence of 1 mol % of $PdCl_2$, the reaction mixture contained 2-ethyl-3,5-dimethylpyridine (**I**) and *N*,*N*-di(cyclopropyl)propan-1-amine (**IX**) (yield 54 and 25%, respectively; Scheme 6).

Scheme 6.



The remaining amount of cyclopropylamine (~20%) was converted into higher oligomers. In this case, the reaction occurred at a higher temperature than with allylamine, presumably due to the necessity of preliminary isomerization of cyclopropylamine into allylamine. Like allylamine, cyclopropylamine was converted under milder conditions ($PdCl_2$, 120°C, 4.5 h) into *N*-(2-methylpent-2-en-1-ylidene)cyclopropanamine (**X**) in 82% yield. Compound **X** quantitatively yields pyridine **I** in 3 h at 170°C (Scheme 7).

Scheme 7.



Thus 2-ethyl-3,5-dimethylpyridine (**I**) can be synthesized in a high yield (~80%) by catalytic heterocyclization of allylamine, diallylamine, and cyclopropylamine in the presence of $PdCl_2$. The reaction involves intermediate formation of azatriene **III** or azadiene **X**. Our results led us to presume that heterocyclization of allylamine in the presence of palladium complexes can be represented by Scheme 8.

3-Methylpyridine (**VIII**) and 4-ethyl-3,5-dimethylpyridine (**II**) were isolated from reaction mixtures by preparative liquid chromatography. Compound **VIII** was identified by comparing with commercially available 3-methylpyridine, and the structure of **II** was proved by independent synthesis [12]. The structure of the other products was determined on the basis of their ^1H and ^{13}C NMR and mass spectra and published data [6, 10, 13, 14].

EXPERIMENTAL

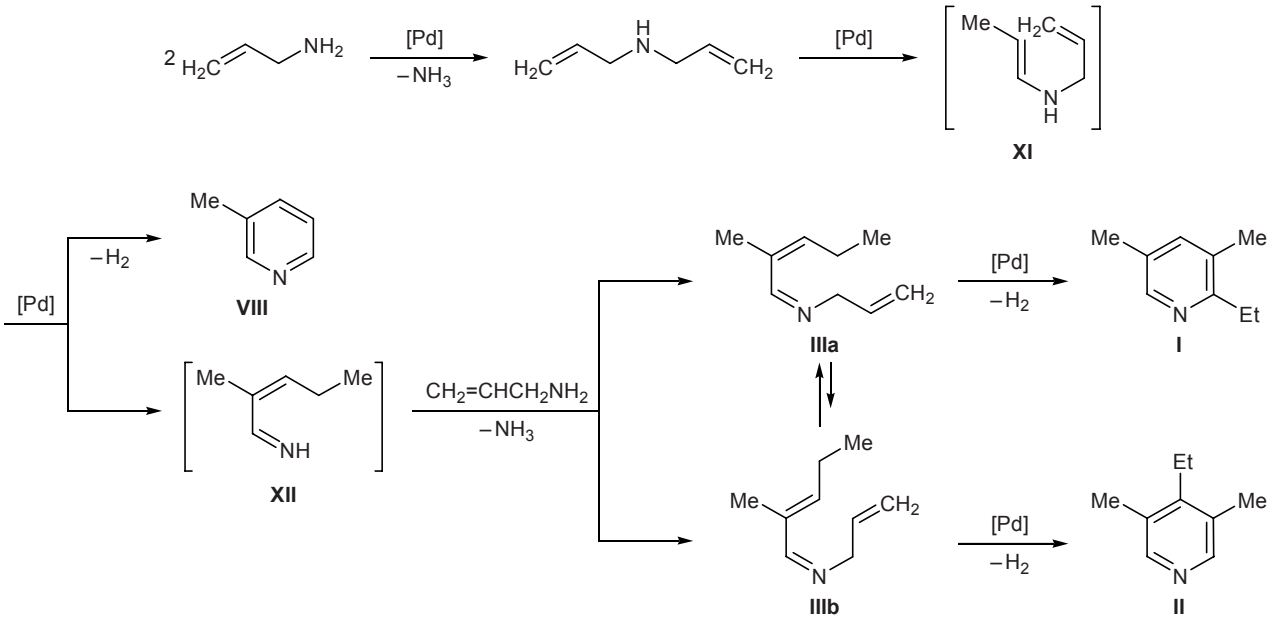
The ^1H and ^{13}C NMR spectra were recorded on Tesla BS-567 (^1H, 100 MHz) and Jeol X-90Q spectrometers (^{13}C, 22.5 MHz) from solutions in $CDCl_3$ using tetramethylsilane as reference. The mass spectra were obtained on a Finnigan 4021 GC–MS system [electron impact, 70 eV; Ultra-29 (PH-S) capillary column, 50000×0.2 mm]. The reaction mixtures were analyzed by GLC on a Chrom-5 chromatograph equipped with a flame-ionization or heat conductivity detector; 300×0.5-cm column packed with SE-30 on Inerton AW-DMCS; carrier gas helium. Preparative liquid chromatography was performed on an HP 1050 instrument with a 18-μl cell; Zorbax C_{18} column, 250×10 mm; eluent acetonitrile–water (70:30), flow rate 3 ml/min.

Allylamine, cyclopropylamine, palladium(II) chloride, and $Pd(acac)_2$ were commercial products (Fluka, Acros); K_2PdCl_4 was synthesized according to the procedure described in [15].

2-Ethyl-3,5-dimethylpyridine (I). A mixture of 3.8 g (66.6 mmol) of allylamine and 0.118 g (0.666 mmol) of $PdCl_2$ was heated for 6 h at 160°C in a 15-cm^3 high-pressure microreactor. The mixture was then distilled under reduced pressure, a fraction with bp 104–108°C (44 mm) being collected. Yield 2.06 g (69%). ^1H NMR spectrum, δ, ppm: 1.20 t (3H, CH_2CH_3, J = 7 Hz), 2.20 s (3H, CH_3), 2.23 s (3H, CH_3), 2.74 q (2H, CH_2, J = 7 Hz), 7.19 s (1H, 4-H), 8.11 s (1H, 6-H).

Heterocyclization of cyclopropylamine was carried out in a similar way at 170°C (reaction time 6 h). Yield of **I** 54%. ^{13}C NMR spectrum, δ_C, ppm: 158.13 (C^2), 129.78 (C^3), 136.70 (C^4), 122.75 (C^5), 146.55 (C^6), 27.81 (CH_2CH_3), 12.59 (CH_2CH_3), 17.47 (CH_3), 18.05 (CH_3). Mass spectrum, m/z (I_{rel}, %): 135 $[M]^+$ (61), 134 (100), 107 (24), 106 (15), 77 (15), 51 (10), 55 (7), 40 (7), 39 (20). Found, %: C 79.43; H 9.52; N 11.05.

Scheme 8.



$C_9H_{13}N$. Calculated, %: C 79.95; H 9.69; N 10.36. *M* 135.21.

A mixture of 2.74 g (20 mmol) of azatriene **III** and 0.035 g (0.2 mmol) of $PdCl_2$ was heated for 4 h at 160°C in a 15-cm^3 high-pressure microreactor. The product was isolated by vacuum distillation, bp 104–106°C (40 mm). Yield 2.69 g (~99%).

Likewise, from 2.65 g of compound **X** (170°C, 3 h) we obtained 2.6 g (~99%) of pyridine **I**.

***N*-(2-Methylpent-2-en-1-ylidene)prop-2-en-1-amine (III).** A mixture of 3.8 g (66.6 mmol) of allylamine and 0.118 g (0.666 mmol) of $PdCl_2$ was heated for 12 h at 100°C in a 30-ml glass ampule. The mixture was distilled under reduced pressure, a fraction with bp 94–96°C (40 mm) being collected. Yield 2.74 g (90%). ^{1}H NMR spectrum, δ, ppm: 7.80 s (1H, 1-H), 5.7–6.2 m (2H, 3-H, C**H**=CH_2), 5.0–5.3 m (2H, CH=C**H**$_2$), 2.26 q (2H, 4-H, *J* = 7 Hz), 1.04 t (3H, 5-H, *J* = 7 Hz), 5.7–6.22 m (3H, CH=CH_2), 4.09 d (2H, NCH_2, *J* = 4 Hz), 1.85 s (3H, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 166.26 (C^1), 92.45 (C^2), 143.37 (C^3), 21.43 (C^4), 11.10 (C^5), 13.18 (CH_3), 62.86 (NCH_2), 136.02 (**C**H=CH_2), 115.08 (CH=**C**H_2). Mass spectrum, *m*/*z* (I_{rel}, %): 137 $[M]^+$ (12), 122 (37), 108 (44), 96 (32), 94 (20), 80 (15), 81 (27), 67 (22), 68 (20), 54 (10), 55 (20), 42 (17), 39 (61), 41 (100). Found, %: C 78.51; H 10.95; N 10.54. $C_9H_{15}N$. Calculated, %: C 78.77; H 11.02; N 10.21. *M* 137.22.

***N*-(2-Methylpent-2-en-1-ylidene)cyclopropanamine (X).** A mixture of 2.5 g (49 mmol) of cyclopropylamine and 0.0869 g (0.49 mmol) of $PdCl_2$ was heated for 4.5 h at 120°C in a 15-cm^3 high-pressure microreactor. The mixture was distilled under reduced pressure, a fraction with bp 115–117°C (40 mm) being collected. Yield 2.05 g (82%). ^{1}H NMR spectrum, δ, ppm: 7.27 s (1H, 1-H), 5.09 t (1H, 3-H, *J* = 7 Hz), 2.14 q (2H, 4-H, *J* = 7 Hz), 0.15–0.40 m (7H, 5-H, CH_2CH_2), 1.52 q (1H, NCH, *J* = 5 Hz), 1.08 s (3H, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 163.32 (C^1), 92.76 (C^2), 141.64 (C^3), 21.48 (C^4), 11.1 (C^5), 13.38 (CH_3), 41.25 (NCH), 8.27 (CH_2CH_2). Mass spectrum, *m*/*z* (I_{rel}, %): 137 $[M]^+$ (22), 122 (49), 120 (7), 109 (32), 108 (100), 107 (10), 105 (10), 80 (17), 94 (78), 95 (15), 67 (56), 41 (44), 39 (32), 81 (29), 68 (20), 53 (17). Found, %: C 78.63; H 10.85; N 10.52. $C_9H_{15}N$. Calculated, %: C 78.77; H 11.02; N 10.21. *M* 137.22.

REFERENCES

1. Xiao, G. and Wu, P., *J. Chin. Chem. Soc*., 1996, vol. 9, p. 50.
2. Goe, G.L., US Patent no. 5061805, 1991.
3. Adams, C.R. and Falbe, J., *Brennstoff Chem*., 1966, vol. 47, p. 184; *Chem. Abstr*., 1966, vol. 65, p. 10557h.
4. Dol'skaya, Yu.S. and Kondrat'eva, G.Ya., *Izv. Akad. Nauk SSSR, Ser. Khim*., 1970, p. 2123.
5. Dol'skaya, Yu.S., Kondrat'eva, G.Ya., and Bratkevich, B.Z., *Izv. Akad. Nauk SSSR, Ser. Khim*., 1978, p. 1446.
6. Falbe, J., Weitkamp, H., and Korte, F., *Tetrahedron Lett*., 1965, vol. 6, no. 31, p. 2677.

7. Bond, J.S., *Usp. Khim*., 1968, vol. 37, p. 56.
8. Murahashi, S.-J. and Makabe, Y., *Tetrahedron Lett*., 1985, vol. 26, p. 5563.
9. Murahashi, S.-J., Makabe, Y., and Kunita, K., *J. Org. Chem*., 1988, vol. 53, p. 4489.
10. Musorin, G.K., *Russ. J. Org. Chem*., 2003, vol. 39, p. 915.
11. Heck, R.F., *Palladium Reagents in Organic Synthesis*, London: Academic, 1985.
12. Kutney, J.P. and Tabata, T., *Can. J. Chem*., 1963, vol. 41, p. 695.
13. Pretch, E., Clerc, T., Seill, J., and Simon, W., *Tables of Spectral Data for Structure Determination of Organic Compounds*, Berlin: Springer, 1983, pp. 90, 190.
14. Maretina, I.A., *Usp. Khim*., 1991, vol. 60, p. 103.
15. Klyuchnikov, N.G., *Rukovodstvo po neorganicheskomu sintezu* (A Guide to Inorganic Synthesis), Moscow: Khimiya, 1965, p. 347.