Brief Communications

A new transformation of aminopyridines upon diazotization in acetonitrile with the formation of *N*-pyridinylacetamides*

A. A. Chudinov,[a] R. S. Dovbnya,[a] E. A. Krasnokutskaya,[a] V. D. Ogorodnikov,[b] and I. L. Filimonova[c]*

[a]*National Research Tomsk Polytechnic University, 30 prosp. Lenina, 634050 Tomsk, Russian Federation*
[b]*Institute of Petroleum Chemistry, Siberian Branch of the Russian Academy of Sciences, 4 prosp. Akademicheskii, 634021 Tomsk, Russian Federation*
[c]*Siberian State Medical University, 2 Moskovskii trakt, 634050 Tomsk, Russian Federation. E-mail: eak@tpu.ru*

Diazotization of aminopyridines upon treatment with $NaNO_2$ and H_3PO_4 in acetonitrile led to the formation of *N*-pyridinylacetamides. This reaction constitutes a convenient and general preparative method for the synthesis of 2-, 3-, and 4-*N*-pyridinylacetamides under mild conditions in good yields. The *in situ* oxidation of the thus obtained *N*-pyridinylacetamides with hydrogen peroxide gave good yields of pyridinylacetamide *N*-oxides.

Key words: aminopyridines, diazotization, *N*-pyridinylacetamides, oxidation.

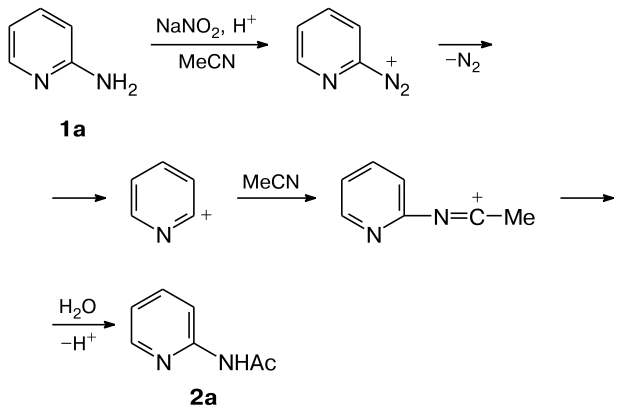
Aminopyridines (especially 2- and 4-amino-substituted derivatives) strongly differ from aromatic amines in their behavior in diazotization reactions,[1] that is mainly related to the instability of pyridinediazonium salts. Earlier, we have shown that the diazotization of aminopyridines in the presence of TsOH or TfOH led to the formation in one step of the corresponding pyridinyl tosylates (PyOTs) and pyridinyl triflates (PyOTf) as a result of a rapid substitution of the diazonium groups with the sulfonic acid moieties.[2—4] Apart from that, we have found[4] that in the case of application of acetonitrile as the solvent in the diazotization of 2-aminopyridine **1a**, *N*-(2-pyridinyl)-acetamide **2a** was formed together with the target 2-pyridyl triflate, *i.e.*, acetonitrile can replace the diazonium group in the pyridine ring, probably, by the Ritter-type reaction (Scheme 1).

The objective of the present work consists in the determination of generality of the found reaction with respect to a number of 2-, 3-, and 4-aminopyridines and development of preparatively acceptable approach to the preparation of *N*-pyridinylacetamides alternative to the known methods.

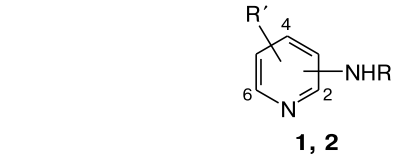
* Based on the materials of the International Congress on the Heterocyclic Chemistry "KOST-2015" (October 17—23, 2015, Moscow, Russia).

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 9, pp. 2312—2314, September, 2016.
1066-5285/16/6509-2312

Scheme 1



We have found that the trituration of a pasty mixture of 1 equiv. of aminopyridines **1a**—**g** with 4 equiv. of $NaNO_2$ and 6 equiv. of H_3PO_4 in a minimum amount of acetonitrile (4—5 equiv.) at room temperature for 1—3 h led to the corresponding pure acetamide derivatives **2a**—**g** (Scheme 2, Table 1). The suggested method is of general character, the yields of the target products **2a**—**g** as a rule are not inferior to those obtained in the acylation which uses traditional acylating agents (acetic anhydride or acetyl chloride).[5—8] A certain advantage of this method is the use of almost stoichiometric amounts of acetonitrile as the reagent and the solvent.



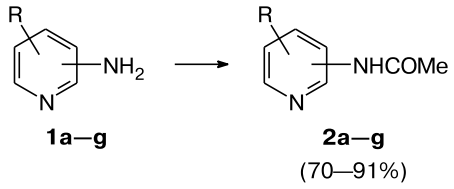
R = H (**1**), Ac (**2**)

Table 1. Synthesis of *N*-pyridinylacetamides **2a**—**g** upon treatment with $NaNO_2$, H_3PO_4 in the presence of acetonitrile at room temperature

1, **2**	NHR[a]	R′	τ/h[b]	Yield (%)	M.p./°C[c]
a	2	H	2	77	164—166 (163—165[7])
b	2	5-Br	1	91	182—183 (181—182[4])
c	2	5-Cl	1	87	170—172 (171—172[11])
d	2	6-Me	2.5	78	89—91 (91—93[7])
e	4	H	2	80	146—147 (146—147[8])
f	3	H	7	0	131—133 (130—132[12])
g	3	2-Cl	3	72	93—94 (93—94[13])

[a] Position of substituent NHR.
[b] Reaction time.
[c] Literature data are given in parentheses.

Scheme 2

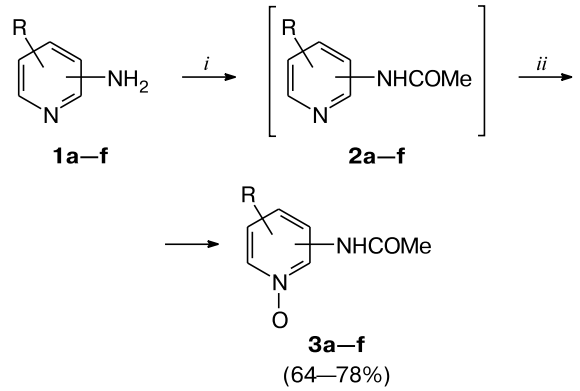


Reagents and conditions: $NaNO_2$, H_3PO_4, in a paste with MeCN, ~20 °C, 1—3 h.

Apart from this, the oxidation of the reaction mixture using a suggested procedure with hydrogen peroxide in acetic acid without isolation and purification of products **2a**—**f** constitutes a simple approach to the preparation of *N*-pyridinylacetamide 1-oxides **3a**—**f** in 64—78% yields calculated on the starting aminopyridines (Scheme 3, Table 2). Compounds **3a**—**f** are widely used for the preparation of valuable aminopyridine 1-oxides,[9—10] the sequence of synthetic steps suggested by us increases availability of these compounds.

In conclusion, we suggested a new general approach to the synthesis of *N*-pyridinylacetamides through the diazotization reaction of aminopyridines upon treatment with sodium nitrite in the presence of a small amount of acetonitrile, which complemented a known spectrum of synthetic procedures directed on the protection of the amino group of aminopyridines in multi-step syntheses.

Scheme 3



Reagents and conditions: *i*. $NaNO_2$, H_3PO_4, in a paste with MeCN, ~20 °C, 1—3 h; *ii*. H_2O_2, AcOH, 80 °C.

Table 2. Synthesis of *N*-pyridinylacetamide 1-oxide **3a—f** from aminopyridines **1a—f** *via* pre-diazotization

2, 3	NHAc[a]	R´	τ/h[b]	Yield (%)	M.p./°C
a	2	H	8	77	141—143 (140—141[14])
b	2	5-Br	7	78	164—167 (165—168[15])
c	2	5-Cl	7	76	150—151 (150—151[16])
d	2	6-Me	7	70	129—131 (130—132[16])
e	4	H	8	64	293—295 (294—296[17])
f	3	H	7	68	208—210 (209—211[18])

[a] Position of substituent NHAc.
[b] Reaction time.
[c] Literature data are given in parentheses.

Experimental

Aminopyridines **1a—g** were commercially available from Sigma-Aldrich, acetonitrile (reagent grade), 98% phosphoric acid (reagent grade, *d* 1.870 g L^{-1}), 30% hydrogen peroxide (reagent grade, *d* 1.40 g L^{-1}). Purification was performed on silica gel for chromatography (40—60 μm). Reaction progress and purity of products were monitored by TLC on Sorbfil-AF 254 plates, using benzene—ethanol (9 : 2) or hexane—ethyl acetate (1 : 3) as eluents. Spots of compounds were visualized under UV light at λ = 254 nm. Compounds were analyzed on an Agilent 7890/5975C chromatograph with a quadrupole mass spectrometer as a detector (EI, 70 eV), carrier gas nitrogen. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-300 spectrometer (300 MHz) in DMSO-d_6, using $SiMe_4$ as an internal standard. Melting points of compounds were determined in a capillary tube, using a MP50 Melting point system heating stage (Mettlertoledo).

Synthesis of *N*-pyridinylacetamides 2a—g upon treatment with a mixture of $NaNO_2$—H_3PO_4 in a paste with acetonitrile (general procedure). Phosphoric acid (0.7 mL, 12 mmol) was added to acetonitrile (0.5 mL, 9.5 mmol), the resulting mixture was cooled to 10—15 °C. Then, a mixture of aminopyridine **1a—g** (2 mmol) and sodium nitrite (0.56 g, 8 mmol) pre-triturated in a mortar was added in small portions at such a rate that allowed us to avoid vigorous liberation of nitrogen oxides. The resulting paste was thoroughly triturated and allowed to stand at 10—15 °C for 10 min and then at 20 °C for the period of time indicated in Table 1. The reaction progress was monitored by TLC (eluent hexane—acetone, 1 : 3) and GC-MS. Upon completion, the reaction mixture was diluted with water, neutralized with $NaHCO_3$, and extracted with ethyl acetate. The organic layer was separated and dried with Na_2SO_4, the solvent was evaporated. Compounds **2a—g** were purified by recrystallization from ethanol. Yields and m.p. of compounds **2a—g** are summarized in Table 1. NMR spectra and m.p. of compounds obtained correspond to the data published for authentic samples.

Preparation of *N*-pyridinylacetamides 2a—f by diazotization of aminopyridines and their subsequent oxidation to *N*-pyridinylacetamide 1-oxides 3a—f (general procedure). Aminopyridines **1a—f** were converted to *N*-pyridinylacetamides **2a—f** upon treatment with the system $NaNO_2$—H_3PO_4—MeCN according to the procedure described above. Without isolation, glacial acetic acid (7 mL) was added to the reaction mixture, which was heated to 80—85 °C. Then, a 30% aqueous solution of hydrogen peroxide (6 mL) was added in portions with continuous stirring. The reaction mixture was stirred at this temperature for 7—8 h. The reaction course was monitored by TLC (eluent hexane—acetone, 1 : 3) and GC-MS. Upon reaction completion, the reaction mixture was neutralized with 10% aqueous solution of $NaHCO_3$ and extracted with dichloromethane (2×30 mL). Compounds **3a—f** were purified by column chromatography (dichloromethane). Yields and m.p. of *N*-oxides **3a—f** are summarized in Table 2. NMR spectra and m.p. of synthesized compounds correspond to the data published for authentic samples.

This work was financially supported by the Russian Foundation for Basic Research (Project No. 14-03-00743a), the analytical part of the work was financially supported by the Ministry of Education and Science of the Russian Federation (State Contract "Science", Project No. 2387).

References

1. R. N. Butler, *Chem. Rev.*, 1975, **75**, 241.
2. A. N. Tretjakov, E. A. Krasnokutskaya, D. A. Gorluschko, V. D. Filimonov, *Tetrahedron Lett.*, 2011, **52**, 85.
3. E. A. Krasnokutskaya, A. Zh. Kassanova, M. T. Estaeva, V. D. Filimonov, *Tetrahedron Lett.*, 2014, **55**, 3771.
4. E. A. Krasnokutskaya, N. I. Semenischeva, V. D. Filimonov, P. A. Knochel, *Synthesis*, 2007, 81.
5. T. Ross Kelly, F. Lang, *J. Org. Chem.*, 1996, **61**, 4623.
6. C. Helgen, C. Bochet, *Heterocycles*, 2006, **67**, 797.
7. P. Mahajan, J. Mahajan, S. Mhaske, *Syntheses Commun.*, 2013, **43**, 2508.
8. I. N. Azerbaev, I. A. Poplavskaya, R. G. Kurmangalieva, *S. F. Khalilova*, *Chem. Heterocycl. Compd.* (*Engl. Transl.*), 1978, **14**, 1241 [*Khim. Geterotsikl. Soedin.*, 1978, 1525].
9. J. Epsztajn, A. Bieniek, J. Kowalska, *Tetrahedron Lett.*, 1991, **47**, 1697.
10. J. Epsztajn, A. Bieniek, M. Ptotka, K. Suwald, *Tetrahedron Lett.*, 1989, **45**, 7469.
11. CH Pat. 578870; *Chem. Abstr.*, 1976, **80**, 134907.
12. L. Sudha, S. Manogaran, *J. Mol. Struc.,* 1985, **129**, 137.
13. Nan Zheng, *Angew. Chem., Int. Ed.*, 2007, **46**, 7509.
14. M. A. Lipton, *J. Med. Chem.*, 1978, **21**, 874.
15. US Pat. 3163655; *Chem. Abstr.*, 1965, **62**, 10419b.
16. G. Lesher, Sterling Drug Inc., US Pat. 3907798 A, 1975.
17. B. Uno, K. Kano, N. Kaida, *Spectrochimica Acta*, 1989, **45**, 9, 937—943.
18. D. Herz, D. Murty, *J. Org. Chem.*, 1960, **25**, 12, 2242.

Received January 22, 2016;
in revised form June 3, 2016