Chemistry of Heterocyclic Compounds, Vol. 36, No. 5, 2000

HETEROCYCLIZATION IN VILSMEIER–HAACK FORMYLATION OF DIMETHYLAMINO-SUBSTITUTED 2,5-DIARYLOXAZOLES AND 2,5-DIARYL-1,3,4-OXADIAZOLES

L. D. Patsenker, I. G. Ermolenko, I. A. Fedyunyaeva, N. A. Popova, and B. M. Krasovitskii

Keywords: 2,5-diaryl-1,3,4-oxadiazoles, 2,5-diaryloxadiazoles, dimethylamino-substituted derivatives, quinazolinium salts, heterocyclization, hydrolysis, Vilsmeier–Haack reaction.

In Vilsmeier–Haack formylation (heating with $POCl_3$ and DMF) of 4-dimethylaminotoluene [1] and 4-dimethylamino-substituted derivatives of naphthalic acid [2], instead of the expected formyl-substituted derivatives we observed heterocyclization of the intermediate Vilsmeier adducts and formation of quinazolinium salts.

We observed that under the same conditions, 2,5-di(4-dimethylaminophenyl)-1,3,4-oxadiazole (**1**) forms quinazolinium salt **2**. In the case of 5-(4-dimethylaminophenyl)-2-(4-nitrophenyl)oxazole (**3**), along with heterocyclization we observe formylation at the free position of the oxazole ring (compound **4**). In alkaline medium, the quaternized heterocycle is hydrolyzed with formation of methylamino-substituted **5** and **6**. The methylene group of the heterocycle is cleaved in this case as a formaldehyde molecule. 5-(4-Dimethylaminophenyl)-2-(4-nitrophenyl)-1,3,4-oxadiazole (**7**) under the indicated conditions yields quaternary salt, which based on ^{1}H NMR spectra is tentatively assigned the structure of indazolium **8**. Base hydrolysis of the latter leads to the methylamino-substituted derivative **9**.

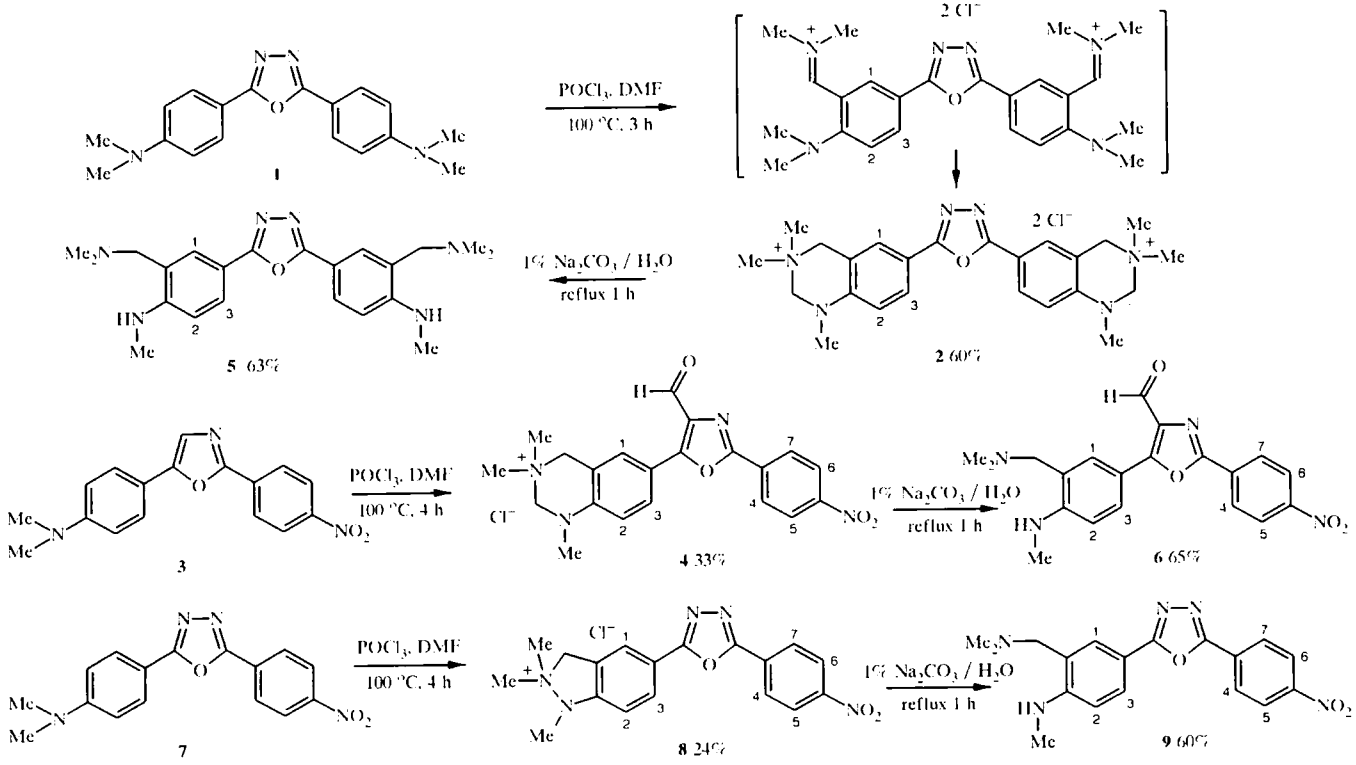
1,3,3-Trimethyl-6-[5-(1,3,3-trimethyl-1,2,3,4-tetrahydroquinazolin-3-ium-6-yl)-1,3,4-oxadiazol-2-yl]-1,2,3,4-tetrahydroquinazolin-3-ium Dichloride (2). Yield 60%; mp 318-320°C (ethanol). ^{1}H NMR spectrum (300 MHz, DMSO-d_6), δ, ppm: 3.16 (12H, s, 2 × $N^+(CH_3)_2$); 3.20 (6H, s, 2 × NCH_3); 4.78 (4H, s, 2 × CH_2); 4.84 (4H, s, 2 × CH_2); 7.14 (2H, d, 2 × 2-H); 7.87 (2H, s, 2 × 1-H); 8.00 (2H, d, 2 × 3-H). Found, %: N 17.12; Cl 14.41. $C_{24}H_{32}N_6OCl_2$. Calculated, %: N 17.11; Cl 14.46.

6-[4-Formyl-2-(4-nitrophenyl)-1,3-oxazol-5-yl]-1,3,3-trimethyl-1,2,3,4-tetrahydroquinazolin-3-ium Chloride (4). Yield 33%; mp 273°C (DMF). ^{1}H NMR spectrum (300 MHz, DMSO-d_6), δ, ppm: 3.17 (6H, s, $N^+(CH_3)_2$; 3.21 (3H, s, NCH_3); 4.81 (2H, s, CH_2); 4.87 (2H, s, CH_2); 7.16 (1H, d, 2-H); 8.10 (1H, s, 1-H); 8.26 (1H, d, 3-H); 8.38 (2H, d, 4,7-H); 8.44 (2H, d, 5,6-H); 10.10 (1H, s, CHO). Found, %: N 12.87; Cl 7.98. $C_{21}H_{21}N_4O_4Cl$. Calculated, %: N 13.07; Cl 8.28.

N,N-Dimethyl-5-[5-(3-dimethylaminomethyl-4-methylaminophenyl)-1,3,4-oxadiazol-2-yl]-2-methylaminophenylmethanamine (5). Yield 63%; mp 183-184°C (benzene–hexane, 1:1). ^{1}H NMR spectrum (300 MHz, DMSO-d_6), δ, ppm: 2.17 (12H, s, 2 × $N(CH_3)_2$); 2.84 (6H, d, 2 × $NHCH_3$); 3.44 (4H, s, 2 × CH_2); 6.57 (2H, s, 2 × NH); 6.69 (2H, d, 2 × 2-H); 7.68 (2H, s, 2 × 1-H); 7.85 (2H, d, 2 × 3-H). Found, %: N 21.12. $C_{22}H_{30}N_6O$. Calculated, %: N 21.32.

Institute of Single Crystals, National Academy of Sciences of Ukraine, Kharkov 310001; e-mail: patsenker@isc.kharkov.com. Translated Khimiya Geterotsiklicheksikh Soedinenii, No. 5, pp. 705-707, May, 2000. Original article submitted March 29, 2000.

0009-3122/00/3605-0623$25.00©2000 KluwerAcademic/Plenum Publishers


POCl3, DMF
100 °C, 3 h
2 Cl⁻
1
5 63%
1% Na2CO3 / H2O
reflux 1 h
2 60%
3
POCl3, DMF
100 °C, 4 h
4 33%
1% Na2CO3 / H2O
reflux 1 h
6 65%
7
POCl3, DMF
100 °C, 4 h
8 24%
1% Na2CO3 / H2O
reflux 1 h
9 60%

5-(3-Dimethylaminomethyl-4-methylaminophenyl)-2-(4-nitrophenyl)-1,3-oxazole-4-carbaldehyde (6). Yield 65%; mp 215-216°C (toluene). ^{1}H NMR spectrum (300 MHz, DMSO-d_6), δ, ppm: 2.18 (6H, s, $N(CH_3)_2$); 2.88 (3H, d, $NH\underline{CH_3}$); 3.47 (2H, s, CH_2); 6.73 (1H, d, 2-H); 6.77 (1H, s, NH); 7.94 (1H, s, 1-H); 8.16 (1H, d, 3-H); 8.34 (2H, d, 4,7-H); 8.40 (2H, d, 5,6-H); 10.06 (1H, s, CHO). Found, %: N 14.53. $C_{24}H_{32}N_6OCl_2$. Calculated, %: N 14.73.

1,2,2-Trimethyl-5-[5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl]-2,3-dihydro-1H-indazol-2-ium Chloride (8). Yield 24%; mp 257.5-258.5°C (ethanol). ^{1}H NMR spectrum (300 MHz, DMSO-d_6), δ, ppm: 2.77 (6H, s, $N^+(CH_3)_2$); 2.86 (3H, s, NCH_3); 4.38 (2H, s, CH_2); 6.83 (1H, d, 2-H); 8.04 (1H, d, 3-H); 8.11 (1H, s, 1-H); 8.34 (2H, d, 4,7-H); 8.46 (2H, d, 5,6-H). Found, %: N 17.80; Cl 8.97. $C_{18}H_{18}N_5O_3Cl$. Calculated, %: N 18.06; Cl 9.14.

N,N-Dimethyl-2-methylamino-5-[5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl]phenylmethanamine (9). Yield 60%; mp 228-230°C (toluene–hexane, 1:1). ^{1}H NMR spectrum (300 MHz, DMSO-d_6), δ, ppm: 2.18 (6H, s, $N(CH_3)_2$); 2.87 (3H, s, $NH\underline{CH_3}$); 3.46 (2H, s, CH_2); 6.67 (1H, s, NH); 6.71 (1H, d, 2-H); 7.74 (1H, s, 1-H); 7.90 (1H, d, 3-H); 8.32 (2H, d, 4,7-H); 8.41 (2H, d, 5,6-H). Found, %: N 19.54. $C_{18}H_{19}N_5O_3$. Calculated, %: N 19.82.

This research was supported by the National Academy of Sciences of Ukraine (grant No. 0198U004256).

REFERENCES

1. B. M. Krasovitskii, L. I. Kormilova, I. G. Ermolenko, L. D. Patsenker, and V. N. Baumer, *Functional Materials*, **4**, 280 (1997).
2. O. Meth-Cohn and D. L. Taylor, *J. Chem. Soc., Chem. Commun.*, 1463 (1995).