Copper-Catalyzed Synthesis of Pentasubstituted Pyridines from *N*-Sulfonyl Ketenimines, 1,1,3,3-Tetramethylguanidine, and Acetylene Dicarboxylates

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Regioselective synthesis of pentasubstituted pyridines has been developed in moderate-to-good yields by the reaction of sulfonyl azides, alkynes, and a dialkyl acetylenedicarboxylate–tetramethylguanidine adduct catalyzed by CuI in MeCN at room temperature.

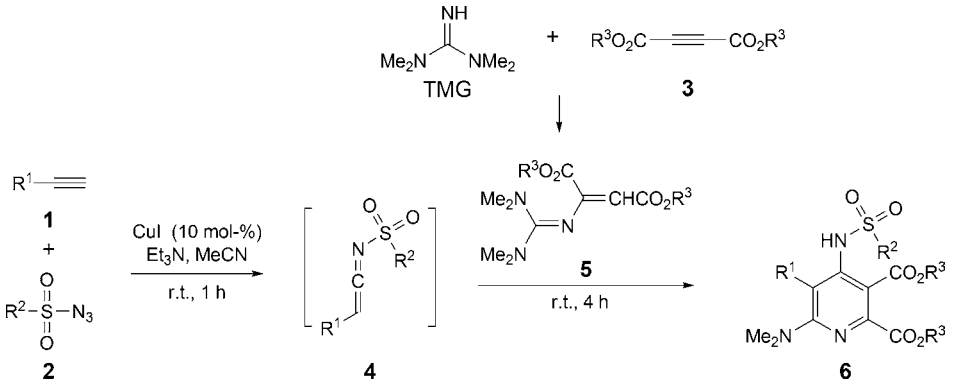
Introduction. – As part of our current studies on heterocyclic synthesis [1–4], we report a simple and efficient procedure for the synthesis of dialkyl 5-aryl(alkyl)-4-(aryl(alkyl)sulfonamido)-6-(dimethylamino)pyridine-2,3-dicarboxylates **6** *via* the Cu-catalyzed tandem reaction of terminal alkynes **1**, sulfonyl azides **2**, 1,1,3,3-tetramethylguanidine (TMG), and dialkyl acetylenedicarboxylates **3** (*Table*).

Results and Discussion. – Initially, *p*-toluenesulfonyl azide (**2a**), phenylacetylene (**1a**), dimethyl acetylenedicarboxylate (**3a**), and TMG were selected as the model substrates. Several catalysts such as CuI, CuBr, CuCl, and Cu powder were tested, with CuI giving the best results. Among several solvents screened, MeCN was the best. When the reaction was performed in MeCN in the presence of 1 equiv. of Et_3N at room temperature for 8 h, it was found that product **6a** was obtained in 88% yield (*Table*). Thus, the optimized reaction conditions used were CuI (10 mol-%), alkyne (1 mmol), sulfonyl azide (1.2 mmol), TMG (1 mmol), and dialkyl acetylenedicarboxylate (1 mmol), in MeCN at room temperature.

The structures of products **6a–6j** were assigned by IR, ^{1}H- and ^{13}C-NMR spectroscopic, and mass spectrometric data. The ^{1}H-NMR spectrum of **6a** exhibited five *singlet*s for Me group (δ(H) 2.58), Me_2N (δ(H) 3.18), MeO (δ(H) 3.79, 3.85), and NH H-atoms (δ(H) 8.39), along with characteristic *multiplet*s for the Ph H-atoms. The ^{13}C-NMR spectrum of **6a** exhibited 19 signals in agreement with the proposed structure. The mass spectrum of **6a** displayed the molecular-ion peak at *m*/*z* 483. The NMR spectra of compounds **6b–6j** are similar to those of **6a**, except for the substituents, which exhibited characteristic signals in the appropriate regions of the corresponding spectra.

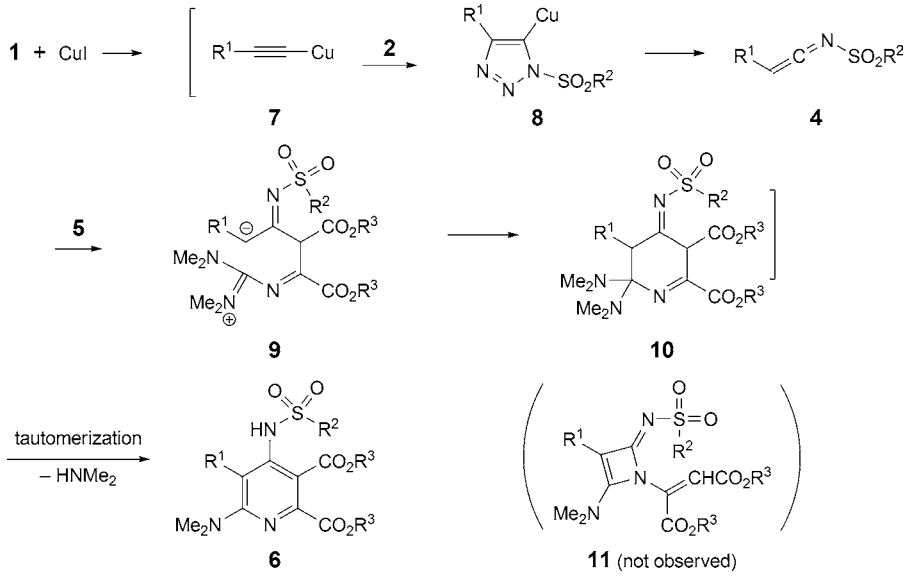
A plausible mechanism for the formation of products **6** is outlined in the *Scheme*. The copper acetylide **7**, formed from **1** and CuI, undergoes a 1,3-dipolar cycloaddition with sulfonyl azide **2** to generate the triazole derivative **8** [5]. This intermediate is converted into *N*-sulfonyl ketenimine **4** [6], which is attacked by the CH moiety of nucleophilic adduct **5** (generated from **3** and TMG) to afford zwiterrionic species **9**.

Table. *Formation of Dialkyl 6-(Dimethylamino)-4-sulfonamidopyridine-2,3-dicarboxylates* **6**



Entry	R^1	R^2	R^3	Product	Yield [%]
1	Ph	4-Me-C_6H_4	Me	**6a**	88
2	Ph	Ph	Me	**6b**	84
3	Ph	Me	Me	**6c**	79
4	Bu	4-Me–C_6H_4	Me	**6d**	67
5	Bu	Ph	Me	**6e**	63
6	Bu	Me	Me	**6f**	60
7	Ph	4-Me–C_6H_4	Et	**6g**	78
8	Ph	Ph	Et	**6h**	75
9	Ph	4-Me–C_6H_4	*t*-Bu	**6i**	74
10	Ph	Me	*t*-Bu	**6j**	70

Scheme



Intermediate **9** undergoes ring formation by *6-exo-trig* mechanism to generate **10**, which is converted to product **6** by elimination of Me_2NH and tautomerization. Since intermediate **5** possesses two nucleophilic sites, formation of an alternative product, namely, *N*-(azet-2(1*H*)-ylidene)sulfonamide **11**, is also possible. Structure **11**, which would be formed by attack of the imino N-atom of **5** on *N*-sulfonyl ketenimine **4**, can be ruled out on the basis of ^{1}H-NMR spectra of the products. Observation of the NH signal (exchangeable in the presence of D_2O) and lack of olefinic CH signal confirm the presence of the pyridine ring system in **6**.

In conclusion, we have developed a regioselective reaction involving *N*-sulfonyl ketenimine intermediates, 1,1,3,3-tetramethylguanidine, and dialkyl acetylenedicarboxylates, which offers a new route for the synthesis of pentasubstituted pyridine derivatives in moderate-to-good yields.

Experimental Part

General. All chemicals were obtained commercially and used without further purification. IR Spectra: *Shimadzu-IR-460* spectrometer; $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR spectra: *Bruker DRX-500 Avance* instrument at 500.1 and 125.7 MHz, resp.; δ in ppm rel. to Me_4Si as internal standard, J in Hz. EI-MS: *Finnigan-MAT-8430* EI-MS mass spectrometer; at 70 eV; in *m/z* (rel. %). Elemental analyses: *Vario EL III CHNOS* elemental analyzer.

General Procedure for the Preparation of Compounds **6**. 1,1,3,3-Tetramethylguanidine (TMG; 0.103 g, 1 mmol) and acetylenedicarboxylate **3** (1 mmol) were dissolved in MeCN (2 ml) and stirred for 1 h. Then, a mixture of the sulfonyl azide **2** (1.2 mmol), alkyne **1** (1 mmol), CuI (0.1 mmol), and Et_3N (1 mmol) in MeCN (3 ml) were added and stirred at r.t. under N_2. After completion of the reaction (*ca.* 4 h; TLC (AcOEt/hexane 1:3) monitoring), the mixture was diluted with CH_2Cl_2 (2 ml) and an aq. NH_4Cl soln. (3 ml), stirred for 30 min, and the layers were separated. The aq. layer was extracted with CH_2Cl_2 (3×3 ml), and the combined org. fractions were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2 (230–400 mesh; *Merck*); hexane/AcOEt 3:1) to give the product.

Dimethyl 6-(Dimethylamino)-4-{[(4-methylphenyl)sulfonyl]amino}-5-phenylpyridine-2,3-dicarboxylate (**6a**). Yield: 0.42 g (88%). Red crystals. M.p. 134–136°. IR (KBr): 3555, 1756, 1509, 1423, 1256, 1198, 1034. ^{1}H-NMR: 2.58 (*s*, Me); 3.18 (*s*, Me_2N); 3.79 (*s*, MeO); 3.85 (*s*, MeO), 7.25–7.30 (*m*, 3 arom. H); 7.60 (*d*, $^3J = 8.0$, 2 arom. H); 7.73 (*d*, $^3J = 7.6$, 2 arom. H); 8.06 (*d*, $^3J = 8.0$, 2 arom. H); 8.39 (*s*, NH). ^{13}C-NMR: 29.0 (Me); 41.1 (Me_2N); 52.9 (MeO); 54.8 (MeO); 124.4 (C); 127.7 (C); 128.9 (2 CH); 129.7 (2 CH); 129.9 (C); 130.1 (CH); 130.5 (2 CH); 133.8 (2 CH); 142.9 (C); 144.8 (C); 145.9 (C); 152.7 (C); 156.6 (C); 169.0 (C); 171.0 (C). EI-MS: 483 (M^+, 3), 439 (27), 365 (9), 313 (16), 170 (25), 155 (100), 91 (70), 77 (54), 59 (21). Anal. calc. for $C_{24}H_{25}N_3O_6S$ (483.15): C 59.61, H 5.21, N 8.69; found: C 59.49, H 5.24, N 8.72.

Dimethyl 6-(Dimethylamino)-5-phenyl-4-[(phenylsulfonyl)amino]pyridine-2,3-dicarboxylate (**6b**). Yield: 0.39 g (84%). Red crystals. M.p. 115–118°. IR (KBr): 3445, 1732, 1527, 1405, 1273, 1143, 1085. ^{1}H-NMR: 3.12 (*s*, Me_2N); 3.77 (*s*, MeO); 3.81 (*s*, MeO); 7.27–7.34 (*m*, 3 arom. H); 7.48 (*d*, $^3J = 7.2$, 2 arom. H); 7.64 (*t*, $^3J = 8.0$, 2 arom. H); 7.76 (*t*, $^3J = 8.0$, 1 arom. H); 8.05 (*d*, $^3J = 8.0$, 2 arom. H); 8.32 (*s*, NH). ^{13}C-NMR: 40.3 (Me_2N); 52.8 (MeO); 54.1 (MeO); 123.2 (C); 127.4 (C); 128.1 (2 CH); 129.5 (2 CH); 129.8 (C); 130.0 (CH); 130.1 (2 CH); 133.2 (2 CH); 136.5 (CH); 143.5 (C); 145.4 (C); 151.9 (C); 154.9 (C); 167.3 (C); 169.9 (C). EI-MS: 469 (M^+, 2), 425 (12), 392 (16), 351 (28), 141 (100), 77 (52), 44 (25). Anal. calc. for $C_{23}H_{23}N_3O_6S$ (469.13): C 58.84, H 4.94, N 8.95; found: C 58.43, H 5.00, N 9.02.

Dimethyl 6-(Dimethylamino)-4-[(methylsulfonyl)amino]-5-phenylpyridine-2,3-dicarboxylate (**6c**). Yield: 0.32 g (79%). Red-orange crystals. M.p. 99–102°. IR (KBr): 3446, 1720, 1650, 1539, 1442, 1274, 1148, 1085. ^{1}H-NMR: 2.97 (*s*, Me); 3.09 (*s*, Me_2N); 3.69 (*s*, MeO); 3.81 (*s*, MeO); 7.34–7.56 (*m*, 3 arom. H); 7.51 (*d*, $^3J = 7.3$, 2 arom. H); 8.54 (*s*, NH). ^{13}C-NMR: 36.5 (Me); 42.9 (Me_2N); 54.3 (MeO); 56.4

(MeO); 123.2 (C); 129.5 (2 CH); 130.0 (CH); 133.3 (2 CH); 135.1 (C); 140.3 (C); 149.2 (C); 152.1 (C); 154.5 (C); 166.9 (C); 169.3 (C). EI-MS: 407 (M^+, 2), 363 (21), 330 (14), 289 (34), 94 (100), 77 (65). Anal. calc. for $C_{18}H_{21}N_3O_6S$ (407.12): C 53.06, H 5.20, N 10.31; found: C 53.42, H 5.25, N 10.37.

Dimethyl 5-Butyl-6-(dimethylamino)-4-{[(4-methylphenyl)sulfonyl]amino}pyridine-2,3-dicarboxylate (**6d**). Yield: 0.31 g (67%). Redish oil. IR (KBr): 3435, 1711, 1651, 1538, 1397, 1276, 1147, 1084. ^{1}H-NMR: 0.92 (*t*, ^3J = 6.8, Me), 1.43–1.50 (*m*, 2 CH_2); 2.19 (*t*, ^3J = 6.8, CH_2); 2.39 (*s*, Me); 3.07 (*s*, Me_2N); 3.77 (*s*, MeO); 3.88 (*s*, MeO); 7.25 (*d*, ^3J = 7.9, 2 arom. H); 7.92 (*d*, ^3J = 7.9, 2 arom. H); 8.48 (*s*, NH). ^{13}C-NMR: 14.7 (Me); 19.2 (CH_2); 22.8 (CH_2); 22.9 (CH_2) 31.7 (Me); 42.4 (Me_2N); 52.9 (MeO); 54.3 (MeO); 122.3 (C); 125.7 (2 CH); 130.5 (2 CH); 134.1 (C); 140.3 (C); 142.7 (C); 143.1 (C); 148.1 (C); 154.3 (C); 164.2 (C); 169.1 (C). EI-MS: 463 (M^+, 2), 406 (7), 345 (20), 293 (41), 155 (100), 91 (71), 57 (40). Anal. calc. for $C_{22}H_{29}N_3O_6S$ (463.18): C 57.00 H 6.31, N 9.06; found: C 57.29, H 6.30, N 8.98.

Dimethyl 5-Butyl-6-(dimethylamino)-4-[(4-phenylsulfonyl)amino]pyridine-2,3-dicarboxylate (**6e**). Yield: 0.28 g (63%). Reddish oil. IR (KBr): 3221, 1717, 1649, 1537, 1277, 1146, 1085. ^{1}H-NMR: 0.95 (*t*, ^3J = 6.9, Me); 1.49–1.52 (*m*, 2 CH_2); 2.16 (*t*, ^3J = 6.9, CH_2); 3.03 (*s*, Me_2N); 3.75 (*s*, MeO); 3.86 (*s*, MeO); 7.63 (*d*, ^3J = 7.9, 2 arom. H); 7.74 (*t*, ^3J = 7.9, 2 arom. H); 7.90 (*t*, ^3J = 7.9, 1 arom. H); 7.93 (*s*, NH). ^{13}C-NMR: 14.6 (Me); 19.2 (CH_2); 22.9 (CH_2); 31.6 (CH_2); 33.3 (Me_2N); 52.7 (MeO); 53.0 (MeO); 127.3 (2 CH); 130.9 (2 CH); 132.4 (C); 133.9 (C); 136.5 (CH); 145.5 (C); 151.5 (C); 154.3 (C); 159.4 (C); 164.2 (C); 168.9 (C). EI-MS: 449 (M^+, 4), 392 (6), 293 (20), 156 (32), 141 (100), 77 (63), 57 (22). Anal. calc. for $C_{21}H_{27}N_3O_6S$ (449.16): C 56.11, H 6.05, N 9.35; found: C 56.41, H 6.08, N 9.39.

Dimethyl 5-Butyl-6-(dimethylamino)-4-[(methylsulfonyl)amino]pyridine-2,3-dicarboxylate (**6f**). Yield: 0.23 g (60%). Redish oil. IR (KBr): 3261, 1713, 1652, 1540, 1440, 1279, 1149, 1084. ^{1}H-NMR: 0.92 (*t*, ^3J = 6.9, Me); 1.26–1.44 (*m*, 2 CH_2); 2.20 (*t*, ^3J = 6.9, CH_2); 3.05 (*s*, Me); 3.18 (*s*, Me_2N); 3.37 (*s*, MeO); 3.81 (*s*, MeO); 8.34 (*s*, NH). ^{13}C-NMR: 14.7 (Me); 19.2 (CH_2); 23.0 (2 CH_2); 32.4 (Me); 41.9 (Me_2N); 54.1 (MeO); 56.8 (MeO); 120.8 (C); 143.2 (C); 148.1 (C); 153.0 (C); 153.7 (C); 168.8 (C); 171.9 (C). EI-MS: 387 (M^+, 6), 343 (10), 269 (15), 143 (25), 94 (100), 59 (42), 57 (24). Anal. calc. for $C_{16}H_{25}N_3O_6S$ (387.45): C 49.60, H 6.50, N 10.85; found: C 50.01, H 6.54, N 10.83.

Diethyl 6-(Dimethylamino)-4-{[(4-methylphenyl)sulfonyl]amino}-5-phenylpyridine-2,3-dicarboxylate (**6g**). Yield: 0.40 g (78%). Red-orange crystals. M.p. 143–146°. IR (KBr): 3448, 1728, 1459, 1383, 1268, 1151, 1184. ^{1}H-NMR: 1.32 (*t*, ^3J = 6.9, Me); 1.34 (*t*, ^3J = 6.9, Me); 2.39 (*s*, Me); 2.98 (*s*, Me_2N); 4.25 (*q*, ^3J = 6.9, CH_2O); 4.28 (*q*, ^3J = 6.9, CH_2O); 7.25–7.27 (*m*, 3 arom. H); 7.41 (*d*, ^3J = 7.5, 2 arom. H); 7.48 (*d*, ^3J = 7.9, 2 arom. H); 7.92 (*d*, ^3J = 7.9, 2 arom. H); 8.27 (*s*, NH). ^{13}C-NMR: 15.2 (Me); 15.4 (Me); 34.2 (Me); 39.8 (Me_2N); 61.8 (CH_2O); 63.5 (CH_2O); 123.2 (C); 128.1 (2 CH); 129.5 (2 CH); 129.9 (CH); 130.3 (C); 131.5 (2 CH); 133.2 (2 CH); 142.7 (C); 142.9 (C); 148.0 (C); 153.8 (C); 157.5 (C); 159.7 (C); 167.3 (C); 169.2 (C). EI-MS: 511 (M^+, 4), 433 (9), 310 (11), 155 (100), 91 (42), 77 (40), 73 (21). Anal. calc. for $C_{26}H_{29}N_3O_6S$ (511.59): C 61.04, H 5.71, N 8.21; found: C 61.37, H 5.80, N 8.16.

Diethyl 6-(Dimethylamino)-5-phenyl-4-[(phenylsulfonyl)amino]pyridine-2,3-dicarboxylate (**6h**). Yield: 0.37 g (75%). Red-orange crystals. M.p. 140–142°. IR (KBr): 3442, 1717, 1644, 1531, 1402, 1277, 1144, 1085, 1034. ^{1}H-NMR: 1.33 (*t*, ^3J = 6.9, Me); 1.37 (*t*, ^3J = 6.9, Me); 3.08 (*s*, Me_2N); 4.26 (*q*, ^3J = 6.9, CH_2O); 4.29 (*q*, ^3J = 6.9, CH_2O); 7.26–7.27 (*m*, 3 arom. H); 7.50 (*d*, ^3J = 7.6, 2 arom. H); 7.64 (*t*, ^3J = 7.9, 2 arom. H); 7.75 (*t*, ^3J = 7.9, 2 arom. H); 8.05 (*d*, ^3J = 7.9, 2 arom. H); 8.45 (*s*, NH). ^{13}C-NMR: 15.2 (2 Me); 35.2 (Me_2N); 61.8 (CH_2O); 63.5 (CH_2O); 123.2 (C); 127.1 (CH); 128.1 (2 CH); 129.5 (2 CH); 129.8 (C); 129.9 (CH); 130.9 (2 CH); 131.1 (CH); 136.5 (2 CH); 145.5 (C); 153.0 (C); 157.1 (C); 159.6 (C); 166.9 (C); 168.3 (C). EI-MS: 497 (M^+, 2), 420 (11), 351 (29), 156 (22), 141 (100), 77 (40), 73 (31), 44 (32). Anal. calc. for $C_{25}H_{27}N_3O_6S$ (497.56): C 60.35, H 5.47, N 8.45; found: C 60.52, H 5.41, N 8.42.

Bis(1,1-dimethylethyl) 6-(Dimethylamino)-4-{[(4-methylphenyl)sulfonyl]amino}-5-phenylpyridine-2,3-dicarboxylate (**6i**). Yield: 0.42 g (74%). Red-orange crystals. M.p. 132–135°. IR (KBr): 3345, 1718, 1637, 1548, 1404, 1283, 1151, 1087. ^{1}H-NMR: 1.21 (*s*, Me_3C); 1.24 (*s*, Me_3C); 2.48 (*s*, Me); 3.05 (*s*, Me_2N); 7.25 (*m*, 3 arom. H); 7.34 (*d*, ^3J = 7.5, 2 arom. H); 7.49 (*d*, ^3J = 7.9, 2 arom. H); 7.78 (*d*, ^3J = 7.9, 2 arom. H); 8.33 (*s*, NH). ^{13}C-NMR: 26.5 (Me_3C); 27.8 (Me_3C); 34.8 (Me); 40.3 (Me_2N); 79.3 (Me_3C); 80.9 (Me_3C); 123.2 (C); 127.3 (2 CH); 128.1 (CH); 129.5 (2 CH); 129.9 (C); 130.3 (C); 130.6 (C); 131.5 (2 CH); 133.2 (2 CH); 157.0 (C); 158.3 (C); 159.4 (C); 167.2 (C); 170.1 (C); 173.2 (C). EI-MS: 567 (M^+, 6), 490 (25), 394 (21), 170 (36), 155 (100), 101 (65), 91 (40). Anal. calc. for $C_{30}H_{37}N_3O_6S$ (567.70): C 63.47, H 6.57, N 7.40; found: C 63.76, H 6.59, N 7.47.

Bis(1,1-dimethylethyl) 6-(Dimethylamino)-4-[(methylsulfonyl)amino]-5-phenylpyridine-2,3-dicarboxylate (**6j**). Yield: 0.34 g (70%). Red-orange crystals. M.p. 120–123°. IR (KBr): 3427, 1717, 1521, 1404, 1274, 1150, 1087. ^{1}H-NMR: 1.23 (*s*, *Me*$_3$C); 1.29 (*s*, *Me*$_3$C); 3.02 (*s*, Me); 3.18 (*s*, Me$_2$N); 7.33 (*t*, ^3J = 7.7, 2 arom. H); 7.44 (*d*, ^3J = 7.7, 3 arom. H); 7.58 (*d*, ^3J = 7.7, 2 arom. H); 7.90 (*t*, ^3J = 7.7, 2 arom. H); 8.44 (*s*, NH). ^{13}C-NMR: 26.1 (*Me*$_3$C); 27.3 (*Me*$_3$C); 31.2 (Me); 40.7 (Me$_2$N); 80.3 (Me$_3$*C*); 81.2 (Me$_3$*C*); 123.2 (C); 127.3 (2 CH); 128.0 (CH); 129.8 (2 CH); 132.5 (CH); 150.1 (C); 154.0 (C); 154.9 (C); 158.3 (C); 167.0 (C); 169.8 (C). EI-MS: 491 (M^+, 5), 414 (13), 397 (24), 101 (28), 94 (100), 77 (38), 44 (31). Anal. calc. for $C_{24}H_{33}N_3O_6S$ (491.60): C 58.64, H 6.77, N 8.55; found: C 59.00, H 6.78, N 8.57.

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