Copper-Catalyzed *N*-Arylation of 1,1,3,3-Tetramethylguanidine–Phenyl Isocyanate Adduct

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The synthesis of a novel class of 3-[bis(dimethylamino)methylidene]-1,1-diarylureas *via* a Cu-catalyzed multicomponent reaction of phenyl isocyanate (PhNCO), 1,1,3,3-tetramethylguanidine, and aryl halides is described.

Introduction. – Ureas play a significant role in organic, bioorganic, medicinal, supramolecular, and materials chemistry [1][2]. Urea function is common in biological systems. Substituted ureas have potent inhibiting effects on HIV-1 protease enzyme [3], as well as anticancer [4][5], anticonvulsive, and sedative-hypnotic activities [6][7]. The standard protocols for the preparation of ureas generally involve the use of toxic and highly reactive phosgene ($COCl_2$) and its derivatives [8]. Usually, the synthesis of ureas is achieved through the condensation of amines with isocyanates [9] and carbamates [10], or oxidative carbonylation of amines with CO in the presence of transition-metal catalysts [11].

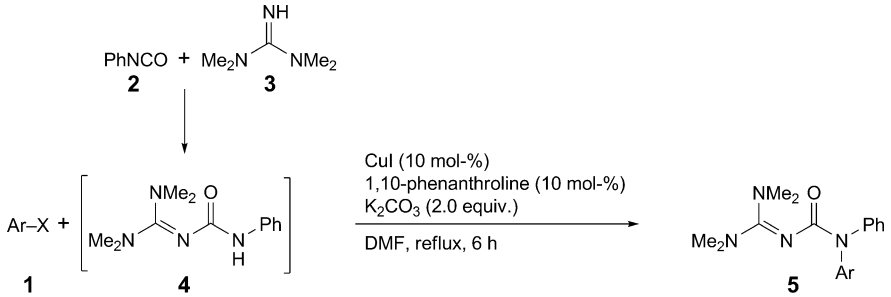
Herein, we report a novel synthesis of 1,1-diaryl-3-[bis(dimethylamino)methylidene]diarylureas **5** *via* Cu-catalyzed *N*-arylation of 1-[bis(dimethylamino)methylidene]-3-phenylurea (**4**; generated *in situ* by addition of 1,1,3,3-tetramethylguanidine (**3**) to phenyl isocyanate (**2**)) by aryl halides **1** (*Scheme*).

Results and Discussion. – Initially, PhI (**1a**), **2**, and **3** were selected as model substrates. Several catalysts such as CuI, CuBr, CuCl, Cu_2O, and Cu powder were tested, with CuI giving the best results. Among several solvents screened, DMF turned out to be the best. Thus, the optimized reaction conditions used were 10 mol-% of CuI as the catalyst, 10 mol-% of 1,10-phenanthroline as the ligand, 2.0 mmol of K_2CO_3 as the base, 1 mmol of **3**, and 1 mmol of **2** in DMF (*Table*).

Using the optimized conditions described above, various 1,1-diaryl-3-[bis(dimethylamino)methylidene]ureas **5** were synthesized by *N*-arylation of tetramethylguanidine–phenyl isocyanate adduct **4** with aryl iodides and aryl bromides bearing an electron-withdrawing substituent. Aryl bromides served as low-yielding substrates compared to aryl iodides (*Scheme*).

Structures of products **5a**–**5h** were determined by IR, ^{1}H- and ^{13}C-NMR, and MS data. The ^{1}H-NMR spectrum of **5a** exhibited two *singlet*s for the Me_2N groups (δ(H) 2.71 and 2.75), along with characteristic *multiplet*s for the Ph H-atoms. The ^{13}C-NMR spectrum of **5a** exhibits twelve signals in agreement with the proposed structure. The

Scheme



	X	Ar	Yield of **5** [%]
1a, **5a**	I	Ph	80
1b, **5b**	I	4-Me–C_6H_4	81
1c, **5c**	I	4-Br–C_6H_4	79
1d, **5d**	I	4-Cl–C_6H_4	75
1e, **5e**	I	4-MeO–C_6H_4	73
1f, **5f**	Br	3-Me–C_6H_4	68
1g, **5g**	Br	3-O_2N–C_6H_4	69
1h, **5h**	Br	Thiophen-2-yl	60

Table. *Optimization of Reaction Conditions for the Formation of* **5a** *from Aryl Iodides, Isocyanates, and 1,1,3,3-Tetramethylguanidine*

Catalyst[a])	Solvent	Yield [%][b])	Catalyst[a])	Solvent	Yield [%][b])
Cu_2O	DMF	41	CuI	Toluene	40
Cu_2O	MeCN	30	CuI	DMSO	21
Cu_2O	Toluene	14	CuI	THF	27
CuCl	DMF	52	CuBr	DMF	58
CuCl	MeCN	40	CuBr	Toluene	27
CuCl	Toluene	31	CuBr	DMSO	19
CuI[c])	DMF	80	Cu	DMF	–
CuI	MeCN	70	Cu	Toluene	–

[a]) 10 mol-% catalyst, unless stated otherwise; 10 mol-% 1,10-phenanthroline. [b]) Reaction time, 6 h. [c]) 5 mol-% catalyst, reaction time, 15 h.

mass spectrum of **5a** displayed the molecular-ion peak at *m*/*z* 310. The NMR spectra of **5b**–**5h** were similar to those of **5a**, except signals of the substituents.

In conclusion, we have developed an experimentally simple, Cu-catalyzed C–N bond-formation reaction for the synthesis of 1,1-diaryl-3-[bis(dimethylamino)methylidene]ureas starting from aryl halides, PhNCO, and 1,1,3,3-tetramethylguanidine. The potential diversity of this type of reaction, and availability of starting materials and catalysts are the main advantages of this methodology.

Experimental Part

General. All chemicals were obtained commercially and used without further purification. M.p.: *Electrothermal-9100* apparatus. Flash column chromatography (FC): silica gel (SiO_2; *Merck*, 230–400

mesh). IR Spectra: *Shimadzu-IR-460* spectrometer; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR spectra: *Bruker DRX-500 Avance* instrument (500.1 and 125.7 MHz for ^1H and ^{13}C, resp.); in $CDCl_3$; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. MS: *Finnigan-MAT-8430EI-MS* mass spectrometer; at 70 eV; in *m*/*z* (rel. %). Elemental analyses: *Vario EL III CHNOS* elemental analyzer; in %.

General Procedure for Preparation of **5**. A mixture of **2** (1 mmol) and **3** (1 mmol) in DMF (2 ml) was stirred for 30 min. Then, a mixture of aryl halide (1 mmol), CuI (0.1 mmol), 1,10-phenanthroline (0.1 mmol), and K_2CO_3 (2.0 mmol) in DMF (3 ml) was slowly added to the first soln. and stirred at 110° under N_2. After completion of the reaction (*ca.* 6 h; TLC (AcOEt/hexane 1:3) monitoring), the mixture was diluted with CH_2Cl_2 (2 ml) and 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 FC (hexane/AcOEt 3:1) to give the product.

3-[Bis(dimethylamino)methylidene]-1,1-diphenylurea (**5a**). Yield: 0.25 g (80%). Cream powder. M.p. 119–121°. IR (KBr): 2041, 1647, 1549, 1445, 1377, 1179, 1075. ^1H-NMR: 2.71 (*s*, Me_2N); 2.75 (*s*, Me_2N); 7.06–7.12 (*m*, 5 arom. H); 7.14–7.19 (*m*, 3 arom. H); 7.26 (*t*, $^3J = 7.4$, 2 arom. H). ^{13}C-NMR: 42.3 (Me_2N); 46.1 (Me_2N); 122.3 (C); 124.6 (C); 125.6 (2 CH); 126.2 (2 CH); 127.3 (CH); 127.9 (CH); 128.4 (2 CH); 129.5 (2 CH); 158.4 (C); 162.4 (C). MS: 310 (2, M^+), 266 (6), 233 (12), 196 (19), 168 (43), 114 (100), 77 (51), 44 (31). Anal. calc. for $C_{18}H_{22}N_4O$ (310.18): C 69.65, H 7.14, N 18.05; found: C 69.46, H 7.19, N 18.13.

3-[Bis(dimethylamino)methylidene]-1-(4-methylphenyl)-1-phenylurea (**5b**). Yield: 0.26 g (81%). Cream powder. M.p. 126–128°. IR (KBr): 2049, 1591, 1497, 1409, 1303, 1230, 1152, 1021. ^1H-NMR: 2.13 (*s*, Me); 2.67 (*s*, Me_2N); 2.77 (*s*, Me_2N); 6.75 (*d*, $^3J = 7.6$, 2 arom. H); 7.05–7.13 (*m*, 5 arom. H); 7.38 (*d*, $^3J = 7.6$, 2 arom. H). ^{13}C-NMR: 30.0 (Me); 41.3 (Me_2N); 46.2 (Me_2N); 122.6 (C); 124.2 (2 CH); 126.1 (2 CH); 127.6 (C); 129.1 (CH); 131.1 (2 CH); 136.1 (2 CH); 137.6 (C); 159.4 (C); 162.3 (C). MS: 324 (3, M^+), 247 (3), 233 (21), 210 (17), 142 (31), 114 (100), 91 (71), 77 (50), 44 (31). Anal. calc. for $C_{19}H_{24}N_4O$ (324.20): C 70.34, H 7.46, N 17.27; found: C 70.61, H 7.39, N 17.33.

3-[Bis(dimethylamino)methylidene]-1-(4-bromophenyl)-1-phenylurea (**5c**). Yield: 0.31 g (79%). Cream powder. M.p. 133–135°. IR (KBr): 2029, 1659, 1597, 1400, 1378, 1271, 1111, 1091. ^1H-NMR: 2.61 (*s*, Me_2N); 2.70 (*s*, Me_2N); 6.99 (*d*, $^3J = 7.6$, 2 arom. H); 7.11–7.19 (*m*, 5 arom. H); 7.42 (*d*, $^3J = 7.6$, 2 arom. H). ^{13}C-NMR: 42.3 (Me_2N); 46.5 (Me_2N); 122.6 (C); 124.4 (2 CH); 126.0 (2 CH); 127.0 (CH); 129.6 (C); 130.1 (2 CH); 133.0 (C); 138.0 (2 CH); 158.4 (C); 162.8 (C). MS: 388 (2, M^+), 311 (11), 273 (14), 245 (28), 154 (100), 142 (31), 114 (87), 44 (29). Anal. calc. for $C_{18}H_{21}BrN_4O$ (388.29): C 55.54, H 5.44, N 14.39; found: C 55.79, H 5.50, N 14.45.

3-[Bis(dimethylamino)methylidene]-1-(4-chlorophenyl)-1-phenylurea (**5d**). Yield: 0.26 g (75%). Cream powder. M.p. 140–143°. IR (KBr): 2089, 1640, 1598, 1349, 1228, 1022. ^1H-NMR: 2.65 (*s*, Me_2N); 2.77 (*s*, Me_2N); 7.02 (*d*, $^3J = 7.6$, 2 arom. H); 7.16 (*d*, $^3J = 7.3$, 2 arom. H); 7.26–7.31 (*m*, 3 arom. H); 7.56 (*d*, $^3J = 7.6$, 2 arom. H). ^{13}C-NMR: 42.0 (Me_2N); 46.4 (Me_2N); 122.0 (C); 123.0 (2 CH); 124.2 (2 CH); 125.0 (C); 127.9 (CH); 133.0 (2 CH); 138.1 (2 CH); 140.0 (C); 159.4 (C); 162.7 (C). MS: 344 (5, M^+), 267 (11), 233 (8), 142 (61), 114 (45), 111 (100), 77 (34), 44 (20). Anal. calc. for $C_{18}H_{21}ClN_4O$ (344.14): C 62.69, H 6.14, N 16.25; found: C 62.96, H 6.16, N 16.34.

3-[Bis(dimethylamino)methylidene]-1-(4-methoxyphenyl)-1-phenylurea (**5e**). Yield: 0.25 g (73%). Cream powder. M.p. 143–145°. IR (KBr): 2049, 1674, 1540, 1450, 1372, 1277, 1188, 1040. ^1H-NMR: 2.80 (*s*, Me_2N); 2.91 (*s*, Me_2N); 3.52 (*s*, MeO); 7.00 (*d*, $^3J = 7.7$, 2 arom. H); 7.11–7.19 (*m*, 5 arom. H); 7.42 (*d*, $^3J = 7.7$, 2 arom. H). ^{13}C-NMR: 42.0 (Me_2N); 46.7 (Me_2N); 55.7 (MeO); 122.3 (C); 124.3 (2 CH); 124.8 (2 CH); 125.5 (2 CH); 127.3 (CH); 129.9 (C); 139.0 (2 CH); 140.0 (C); 157.4 (C); 161.6 (C). MS: 340 (6, M^+), 296 (11), 263 (9), 233 (25), 114 (65), 107 (100), 44 (29). Anal. calc. for $C_{19}H_{24}N_4O_2$ (340.19): C 67.04, H 7.11, N 16.46; found: C 67.36, H 7.17, N 16.49.

3-[Bis(dimethylamino)methylidene]-1-(3-methylphenyl)-1-phenylurea (**5f**). Yield: 0.22 g (68%). Cream powder. M.p. 119–121°. IR (KBr): 2027, 1678, 1559, 1411, 1366, 1222, 1177, 1070. ^1H-NMR: 2.17 (*s*, Me); 2.78 (*s*, Me_2N); 2.80 (*s*, Me_2N); 7.22–7.25 (*m*, 2 arom. H); 7.33 (*d*, $^3J = 7.5$, 2 arom. H); 7.38–7.41 (*m*, 3 arom. H); 7.47 (*d*, $^3J = 7.7$, 1 arom. H); 7.56 (*d*, $^3J = 7.7$, 1 arom. H). ^{13}C-NMR: 31.0 (Me); 42.2 (Me_2N); 46.4 (Me_2N); 122.5 (CH); 123.0 (CH); 124.2 (2 CH); 125.3 (2 CH); 126.0 (CH); 126.9 (C); 128.0 (C); 130.1 (CH); 131.9 (C); 134.9 (CH); 157.4 (C); 162.4 (C). MS: 324 (1, M^+), 247 (9), 233 (19),

142 (23), 114 (100), 91 (44), 77 (25), 44 (45). Anal. calc. for $C_{19}H_{24}N_4O$ (324.20): C 70.34, H 7.46, N 17.27; found: C 70.61, H 7.39, N 17.34.

3-[Bis(dimethylamino)methylidene]-1-(3-nitrophenyl)-1-phenylurea (**5g**). Yield: 0.24 g (69%). Pale-yellow powder. M.p. 141–143°. IR (KBr): 2039, 1615, 1528, 1459, 1378, 1222, 1191, 1069. ^{1}H-NMR: 2.71 (*s*, Me_2N); 2.80 (*s*, Me_2N); 7.22–7.28 (*m*, 2 arom. H), 7.32–7.37 (*m*, 3 arom. H); 7.42 (*d*, $^3J = 7.5$, 2 arom. H); 7.62 (*d*, $^3J = 7.9$, 1 arom. H); 7.71 (*d*, $^3J = 7.9$, 1 arom. H). ^{13}C-NMR: 41.7 (Me_2N); 44.8 (Me_2N); 122.5 (CH); 123.7 (2 CH); 124.1 (2 CH); 125.5 (CH); 126.0 (C); 128.0 (CH); 130.2 (C); 132.7 (CH); 134.4 (CH); 147.7 (C); 158.7 (C); 163.9 (C). MS: 355 (3, M^+), 278 (9), 233 (15), 213 (22), 122 (100), 114 (41), 44 (52). Anal. calc. for $C_{18}H_{21}N_5O_3$ (355.16): C 60.83, H 5.96, N 19.71; found: C 61.09, H 5.88, N 19.79.

3-[Bis(dimethylamino)methylidene]-1-phenyl-1-(thiophen-2-yl)urea (**5h**). Yield: 0.19 g (60%). Cream powder. M.p. 125–127°. IR (KBr): 2038, 1666, 1580, 1481, 1366, 1179, 1082. ^{1}H-NMR: 2.76 (*s*, Me_2N); 2.84 (*s*, Me_2N); 6.71 (*dd*, $^3J = 4.6, 4.5$, CH); 6.94 (*dd*, $^3J = 4.6$, $^4J = 2.1$, CH); 7.13 (*dd*, $^3J = 4.6$, $^4J = 2.1$, CH); 7.17–7.23 (*m*, 3 H, Ph); 7.32 (*d*, $^3J = 7.5$, 2 arom. H). ^{13}C-NMR: 41.5 (Me_2N); 45.4 (Me_2N); 123.3 (C); 124.4 (2 CH); 125.6 (C); 125.9 (2 CH); 126.4 (CH); 127.0 (CH); 127.6 (CH); 131.2 (CH); 158.7 (C); 163.9 (C). MS: 316 (1, M^+), 239 (17), 233 (26), 202 (29), 142 (35), 114 (23), 83 (100), 77 (54), 44 (33). Anal. calc. for $C_{16}H_{20}N_4OS$ (316.14): C 60.73, H 6.37, N 17.71; found: C 60.28, H 6.42, N 17.80.

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