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SHORT COMMUNICATION

SYNTHESIS AND CRYSTAL STRUCTURE OF *N*-(3-BENZYLAMINO-2- CYANO-3-METHYLTHIOACRYLYL)-*N′*-(SUBSTITUTED PHENYL)UREAS

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ABSTRACT. Phenylurea groups were introduced into the frame of traditional cyanoacrylate and a series of *N*-(3-benzylamino-2-cyano-3-methylthioacrylyl)-*N′*-(substituted phenyl)ureas were synthesized. All compounds are new and their structures were confirmed by ^{1}H NMR, ^{13}C NMR and mass spectral analyses.

KEY WORDS: Synthesis, Cyanoacrylate, Phenylurea derivatives

INTRODUCTION

The herbicidal activities of cyanoacrylates have been the subject of intense interest in past decades [1-4]. Some phenylurea derivatives have also been used as herbicide [5], such as fluometuron. Cyanoacrylates and phenylurea derivatives both are inhibitors of photosystem II (PSII) electron transport, which inhibit the growth of weeds by disrupting photosynthetic electron transport at a common binding domain on the 32 kD polypeptide of the PSII reaction center [6]. According to the connecting principle of biological activity groups, phenylurea groups are introduced to the frame of cyanoacrylate and novel compounds may exhibit good herbicidal activities. In this paper, we report the synthesis and structure analysis of *N*-(3-benzylamino-2-cyano-3-methylthioacrylyl)- *N′*-(substituted phenyl)ureas. Their NMR analysis, mass spectrum analysis and crystal structure have been investigated.

RESULTS AND DISCUSSION

The preparation route of target compounds is shown in Scheme 1. Substituted phenyl isocyanate (**1**) was obtained from substituted aniline by refluxing with bis(trichloromethyl) carbonate (BTC) in dry ethyl acetate. A solution of isocyanate **1** in acetone was added dropwise to a solution of ammonia in the same solvent at 0-5 ^{o}C afforded substituted phenylurea (**2**) [7-8]. Subsequent treatment of compound **2** with cyanoacetic acid furnished *N*-(2-cyanoacetyl)-*N′*-(substituted phenyl)urea (**3**) [9], *N*-(2-cyano-3,3-dimethylthioacrylyl)-*N′*-(substituted phenl)urea (**4**) was obtained from compound **3** by reacting with KOH and carbon disulfide with dimethyl sulfide as methylation agent. Aminolysis of compound **4** with benzylamine afforded *N*-(3-benzylamino-2-cyano-3-methylthio-acrylyl)-*N′*-(substituted phenyl)urea (**5**) [10-11].

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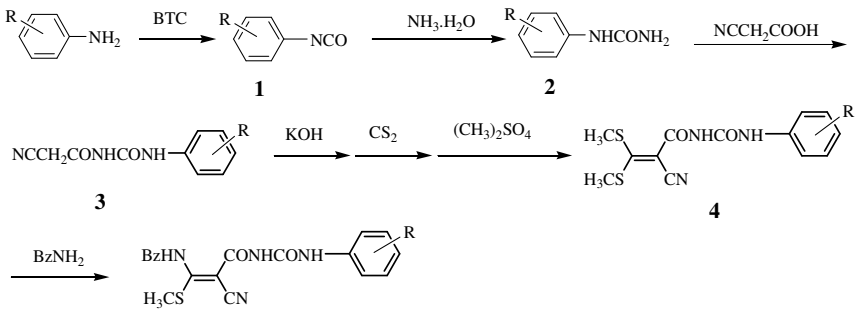
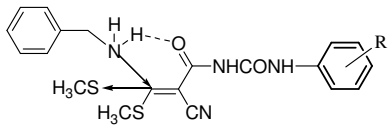


R: H (**5a**), 2-CH_3 (**5b**), 3-CH_3 (**5c**), 4-CH_3 (**5d**), 2-Cl (**5e**), 3-Cl (**5f**), 4-Cl (**5g**), 2-F (**5h**), 4-F (**5i**), 2, 4-F (**5j**), 4-F-3-Cl (**5k**).

Scheme 1. Schematic representation of the preparation of *N*-(3-benzylamino-2-cyano-3-methyl thioacrylyl)-*N'*-(substituted phenyl)urea (**5**).

Benzylamine attacked double bond to form a transition state in which the orientation of benzylamino and ester carbonyl is cis because of the formation of an intramolecular hydrogen bonding (Scheme 2). The configuration of compound **5h** was confirmed by X-ray diffraction analysis and an intramolecular hydrogen bond between the ester carbonyl oxygen and the benzylamino hydrogen atom was demonstrated.



Scheme 2. Mechanism of aminolysis.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 at 500 MHz and 125 MHz, respectively, using a Bruker-500 machine and chemical shifts were reported relative to Me_4Si as internal standard. Mass spectra (EI, 70 eV) were conducted using Shimadzu GCMS-QP 2010 machine. Single crystal structure determination by X-ray diffraction was performed on a Bruker P4 CCD diffractometer. The melting point was measured by YRT-3 Melting Point Tester.

*General synthetic procedure for substituted phenylurea (**2**).* Substituted aniline (54 mmol) was added dropwise to a solution of bis(trichloromethyl) carbonate (8.0 g, 27 mmol) in dry ethyl acetate (30 mL) at 0-5 ^{o}C, the mixture was stirred for 1 h at room temperature and heated under reflux for 5 h, cooled on standing, then solvent was evaporated under reduced pressure to get substituted isocyanate. A solution of substituted isocyanate and acetone (20 mL) was added dropwise to a mixture of ammonia (11 mL, 163 mmol) and acetone (10 mL) at 0-5 ^{o}C, the mixture was stirred for 10 h at room temperature and evaporated under reduced pressure. The residue was washed with water and recrystallized from ethanol.

*General synthetic procedure for N-(2-cyanoacetyl)-N'-(substituted phenyl)urea (**3**).* Ac_2O (5 mL) was added to a mixture of substituted phenylurea (10 mmol) and cyanoacetic acid (1.02 g, 12 mmol), the mixture was heated at 60 °C for 1 h, cooled on standing, the precipitated crystals were filtered off, washed with hexane and recrystallized from ethanol.

*General synthetic procedure for N-(2-cyano-3,3-dimethylthioacrylyl)-N'-(substituted phenyl)urea (**4**).* Compound **3** (3.3 mmol) was added to a mixture of potassium hydroxide powder (0.45 g, 6.6 mmol) and anhydrous acetonitrile (25 mL), the mixture was stirred for 0.5 h, then a solution of carbon disulfide (0.22 mL, 3.6 mmol) in anhydrous acetonitrile (20 mL) was added dropwise at 0-5 °C. The mixture was stirred for 4 h at 25 °C. Then the solution was cooled to 0-5 °C and dimethyl sulfate (0.63 mL, 6.6 mmol) was added. The mixture was stirred for another 4 h at 25 °C and evaporated under reduced pressure, the water (30 mL) were added to the residue, the precipitated solid were filtered off and washed with ethanol and hexane. Compound **4c** was chosen for ^{1}H NMR analysis.

4c. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.27 (s, 3H, C**H**$_3$Ph), 2.58 (s, 3H, SCH_3), 2.71 (s, 3H, SCH_3), 6.86-7.29 (m, 4H, C_6H_4), 8.27 (s, 1H, N**H**Ph), 10.17 (s, 1H, NHCO).

*General synthetic procedure for N-(3-benzylamino-2-cyano-3-methylthioacrylyl)-N'-(substituted phenyl)urea (**5**).* Benzylamine (0.22 mL, 2.0 mmol) was added dropwise to a mixture of compound **4** (1.8 mmol) and ethanol (15 mL) at 0-5 °C. The solution was stirred for 10 h then evaporated under reduced pressure to give crude product. The product was purified by column chromatography on a silica gel.

5a. Yellow solid. Yield 71%. m.p. 126.7-129.0 °C. ^{1}H NMR (DMSO-d_6, 500 MHz), δ: 2.63 (s, 3H, SCH_3), 4.81 (d, J = 5.5 Hz, 2H, C**H**$_2$NH), 7.06-7.50 (m, 10H, 2Ph), 9.22 (s, 1H, N**H**Ph), 10.18 (s, 1H, NHCO), 10.67 (br s, 1H, CH_2N**H**). ^{13}C NMR (DMSO-d_6, 125 MHz), δ: 18.1, 49.7, 74.9, 118.9, 119.6, 123.6, 127.5, 127.8, 128.9, 129.2, 137.5, 138.1, 150.4, 166.9, 173.1. MS (EI, 70 eV) *m/z*(%): 366 (M^+, 5), 319 (7), 274 (3), 231 (2), 119 (4), 91 (100), 65 (13), 39 (3).

5b. Yellow solid. Yield 82%. m.p. 150.0-151.0 °C; ^{1}H NMR (DMSO-d_6, 500 MHz), δ: 2.24 (s, 3H, C**H**$_3$Ph), 2.64 (s, 3H, SCH_3), 4.81 (d, J = 4.5 Hz, 2H, C**H**$_2$NH), 7.02□7.90 (m, 9H, 2Ph), 9.20 (s, 1H, N**H**Ph), 10.16 (s, 1H, NHCO), 10.54 (br s, 1H, CH_2N**H**). ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 17.5, 17.7, 49.6, 74.5, 118.5, 121.1, 123.8, 126.3, 127.1, 127.5, 127.8, 128.6, 130.2, 136.0, 137.2, 150.4, 167.0, 173.0. MS (EI, 70 eV) *m/z*(%): 380 (M^+, 4), 333 (4), 273 (3), 230 (2), 133 (3), 107 (21), 91 (100), 65 (12), 39 (2).

5c. Yellow solid. Yield 70%. m.p. 111.0-113.0 °C. ^{1}H NMR (DMSO-d_6, 500 MHz), δ: 2.28 (s, 3H, C**H**$_3$Ph), 2.63 (s, 3H, SCH_3), 4.81 (d, J = 5.5 Hz, 2H, C**H**$_2$NH), 6.88-7.41 (m, 9H, 2Ph), 9.19 (s, 1H, N**H**Ph), 10.15 (s, 1H, NHCO), 10.66 (br s, 1H, CH_2N**H**). ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 17.8, 21.0, 49.5, 74.8, 116.5, 118.6, 119.8, 124.1, 127.3, 127.6, 128.7, 128.8, 137.3, 137.7, 138.2, 150.1, 166.7, 172.8. MS (EI, 70 eV) *m/z*(%): 380 (M^+, 7), 333 (7), 274 (3), 231 (2), 133 (5), 107 (34), 91 (100), 65 (16), 39 (5).

5d. White solid, Yield 76%. m.p. 111.0-112.5 °C. ^{1}H NMR (DMSO-d_6, 500 MHz), δ: 2.25 (s, 3H, C**H**$_3$Ph), 2.63 (s, 3H, SCH_3), 4.81 (d, J = 5.5 Hz, 2H, C**H**$_2$NH), 7.11-7.41 (m, 9H, 2Ph), 9.10 (s, 1H, N**H**Ph), 10.09 (s, 1H, NHCO), 10.65 (br s, 1H, CH_2N**H**). ^{13}C NMR (DMSO-d_6, 125 MHz), δ: 17.8, 20.3, 49.4, 74.7, 118.5, 119.4, 127.3, 127.5, 128.6, 129.2, 132.4, 135.2, 137.2, 150.0, 166.6, 172.7. MS (EI, 70 eV) *m/z*(%): 380 (M^+, 9), 333 (4), 273 (4), 230 (3), 133 (7), 107 (48), 91 (100), 65 (15), 39 (5).

5e. Yellow solid. Yield 80%. m.p. 171.9-172.9 °C. ^{1}H NMR (DMSO-d_6, 500 MHz), δ: 2.64 (s, 3H, SCH_3), 4.81 (d, *J* = 5.0 Hz, 2H, C**H**$_2$NH), 7.10-8.22 (m, 9H, 2Ph), 9.49 (s, 1H, N**H**Ph), 10.49 (br s, 1H, CH_2N**H**), 10.76 (s ,1H, NHCO). ^{13}C NMR (DMSO-d_6, 125 MHz), δ: 17.7, 49.6, 74.4, 118.4, 121.6, 122.5, 124.5, 127.2, 127.5,127.7, 128.6, 129.2, 134.7, 137.2, 150.3, 166.9, 173.4. MS (EI, 70 eV) *m/z*(%): 400 (M^+, 2), 353 (3), 274 (3), 231 (2), 207 (3), 153 (3), 127 (19), 91 (100), 65 (13), 39 (3).

5f. Yellow needle. Yield 71%. m.p. 148.4-149.4 °C. ^{1}H NMR (DMSO-d_6, 500 MHz), δ: 2.63 (s, 3H, SCH_3), 4.80 (d, *J* = 5.0 Hz, 2H, C**H**$_2$NH), 7.11-7.73 (m, 9H, 2Ph), 9.28 (s, 1H, N**H**Ph), 10.26 (s, 1H, NHCO), 10.68 (br s, 1H, CH_2N**H**). ^{13}C NMR (DMSO-d_6, 125 MHz), δ: 17.9, 49.6, 74.7, 117.9, 118.7, 118.9, 123.1, 127.4, 127.7, 128.8, 130.6, 133.3, 137.3, 139.5, 150.3, 166.6, 173.1. MS (EI, 70 eV) *m/z*(%): 400 (M^+, 2), 353 (2), 274 (3), 231 (2), 207 (2), 153 (3), 127 (18), 91 (100), 65 (15), 39 (2).

5g. Yellow solid. Yield 76%. m.p. 123.0-124.5 °C. ^{1}H NMR (DMSO-d_6, 500 MHz), δ: 2.64 (s, 3H, SCH_3), 4.82 (d, *J* = 5.5 Hz, 2H, C**H**$_2$NH), 7.32-7.55 (m, 9H, 2Ph), 9.29 (s, 1H, N**H**Ph), 10.25 (s, 1H, NHCO), 10.70 (br s, 1H, CH_2N**H**). ^{13}C NMR (DMSO-d_6, 500 MHz), δ: 17.8, 49.6, 74.7, 118.6, 121.0, 127.1, 127.4, 127.7, 128.7, 128.8, 136.9, 137.2, 150.2, 166.6, 172.9. MS (EI, 70 eV) *m/z*(%): 400 (M^+, 2), 353 (1), 273 (4), 230 (2), 207 (3), 153 (4), 127 (20), 91 (100), 65 (16), 39 (3).

5h. White solid. Yield 76%. m.p. 161.0-161.9 °C. ^{1}H NMR (DMSO-d_6, 500 MHz), δ: 2.64 (s, 3H, SCH_3), 4.83 (d, *J* = 5.5 Hz, 2H, C**H**$_2$NH), 7.10-8.17 (m, 9H, 2Ph), 9.43 (s, 1H, N**H**Ph), 10.47 (s, 1H, NHCO), 10.59 (br s, 1H, CH_2N**H**). ^{13}C NMR (DMSO-d_6, 125 MHz), δ: 17.8, 49.5, 74.5, 114.9 (d, *J* = 18.9 Hz), 118.5, 121.4, 124.0 (d, *J* = 7.5 Hz), 124.6 (d, *J* = 3.5 Hz), 125.9 (d, *J* = 10.1 Hz), 127.2, 127.5, 128.6, 137.2, 150.2, 151.3 (d, *J* = 241.0 Hz), 166.8, 173.1. MS (EI, 70 eV) *m/z*(%): 384 (M^+, 4), 337 (7), 274 (6), 231 (4), 137 (4), 111 (30), 91 (100), 65 (13), 39 (3).

5i. White solid. Yield 70%. m.p. 126.0-127.4 °C. ^{1}H NMR (DMSO-d_6, 500 MHz), δ: 2.64 (s, 3H, SCH_3), 4.81 (d, *J* = 5.5 Hz, 2H, C**H**$_2$NH), 7.14-7.53 (m, 9H, 2Ph), 9.24 (s, 1H, N**H**Ph), 10.16 (s, 1H, NHCO), 10.67 (br s, 1H, CH_2N**H**). ^{13}C NMR (DMSO-d_6, 500 MHz), δ: 17.9, 49.5, 74.7, 115.4 (d, *J* = 22.0 Hz), 118.6, 121.3 (d, *J* = 7.5 Hz), 127.4, 127.7, 128.8, 134.2 (d, *J* = 2.0 Hz), 137.3, 150.3, 157.2 (d, *J* = 238.5 Hz), 166.6, 172.9. MS (EI, 70 eV) *m/z*(%): 384 (M^+, 8), 337 (6), 274 (6), 231 (4), 137 (7), 111 (40), 91 (100), 65 (13), 39 (4).

5j. White needle. Yield 77%. m.p. 143.9-144.3 °C. ^{1}H NMR (DMSO-d_6, 500 MHz), δ: 2.64 (s, 3H, SCH_3), 4.82 (d, *J* = 5.5 Hz, 2H, C**H**$_2$NH), 7.07-8.11 (m, 8H, 2Ph), 9.44 (s, 1H, N**H**Ph), 10.35 (s, 1H, NHCO), 10.59 (br s, 1H, CH_2N**H**). ^{13}C NMR (DMSO-d_6, 500 MHz), δ:17.8, 49.6, 74.5, 103.6 (dd, *J* = 3.5, 23.4 Hz), 111.1 (dd, *J* = 18.1, 3.5 Hz), 118.4, 122.4 (dd, *J* = 7.3, 3.5 Hz), 122.8 (d, *J* = 9.4 Hz), 127.2, 127.5, 128.6, 137.2, 150.3, 151.5 (dd, *J* = 231.9, 12.6 Hz), 156.7 (dd, *J* = 230.1, 11.5 Hz), 166.8, 173.1. MS (EI, 70 eV) *m/z*(%): 402 (M^+, 8), 355 (5), 274 (10), 231 (7), 155 (7), 129 (42), 91 (100), 65 (12), 39 (3).

5k. Yellow needle. Yield 65%. m.p. 145.6-147.6 °C. ^{1}H NMR (DMSO-d_6, 500 MHz), δ: 2.65 (s, 3H, SCH_3), 4.82 (d, *J* = 4.0 Hz, 2H, C**H**$_2$NH), 7.31-7.85 (m, 8H, 2Ph), 9.35 (s, 1H, N**H**Ph), 10.23 (s, 1H, NHCO), 10.68 (br s, 1H, CH_2N**H**). ^{13}C NMR (DMSO-d_6, 500 MHz), δ: 17.8, 49.5, 74.7, 116.8 (d, *J* = 21.6 Hz), 118.5, 119.2 (d, *J* = 18.3 Hz), 119.9 (d, *J* = 6.9 Hz), 121.0, 127.3, 127.6, 128.7, 135.1 (d, *J* = 2.8 Hz), 137.1, 150.3, 152.3 (d, *J* = 241.5 Hz), 166.5, 172.9. MS (EI,

70 eV) *m/z*(%): 418 (M^+, 2), 371 (1), 273 (3), 231 (2), 171 (4), 145 (9), 91 (100), 65 (12), 39 (2).

*X-ray diffraction data of N-(3-benzylamino-2-cyano-3-methylthioacrylyl)-N'-(2-fluoro phenyl) urea (**5h**).* The colourless plate crystals of compound **5h** were obtained by slow evaporation of a solution of (**5h**) in acetone at room temperature. All the measurements were performed using graphite monochromatized Mo K_α radiation at 133K, $C_{19}H_{17}FN_4O_2S$, Mr 384.43, triclinic, space group *P1*, a = 0.9242 (2) nm, b = 1.0047 (2) nm, c = 1.1095 (2) nm, α = 73.312 (6)°, β = 66.880 (6)°, γ = 84.295 (7)°, V = 0.9074 (3) nm^3. Z = 2, D_C = 1.407 g/cm^3, μ = 0.211 mm^{-1}, F (000) = 400, R = 0.036, wR = 0.765. The structure was solved by the direct mothod (SHELXS-97) [12] and refined by full-matrix least squares techniques against F^2 (SHELXL-97) [13]. All of the non-hydrogen atoms were anisotropically. The molecular structure of compound **5h** is shown in Figure 1 with displacement ellipsoids drawn at the 50% probability level, all H atoms have been omitted for clarity. Hydrogen bonds for compound **5h** are given in Table 1. The Cambridge Crystallographic Data Centre number code of compound **5h** is 858341.

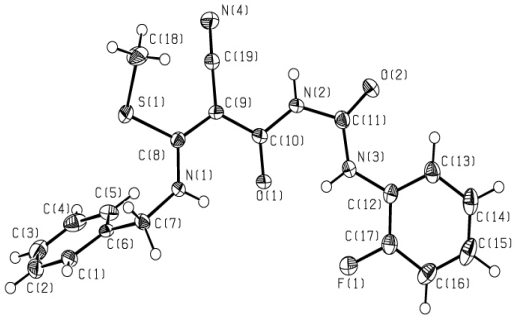


Figure 1. Molecular structure of compound **5h**.

Table 1. Hydrogen bonds for compound **5h**.

D—H…A	*d*(D—H)/nm	*d*(H…A)/nm	*d*(D…A)/nm	∠D—H…A/(°)
N(3)—H(3N)…O(1)	0.0831(15)	0.1907(15)	0.2601(15)	140.3(13)
N(2)—H(2N)…N(4)	0.0855(15)	0.2232(15)	0.3070(16)	166.6(14)
N(1)—H(1N)…O(1)	0.0868(16)	0.1887(16)	0.2602(14)	138.6(14)

Symmetry code: (i) –x, -y+1, -z+2.

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