Synthesis of 4,6-Diaryl-2-cyanoiminopiperidines from *N*-Cyanocinnamamidines

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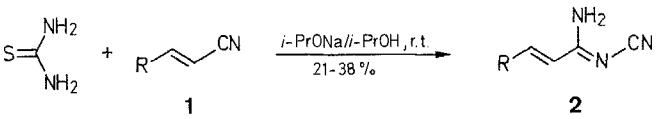
N-Cyanocinnamamidines **2** prepared from thiourea and 3-arylpropenenitriles **1** react with different benzylidene compounds providing a new and simple method for the synthesis of 4,6-diaryl-2-cyanoiminopiperidines **6** and **7**.

Alkyl- and aryl-*N*-cyanoamidines have been used for the synthesis of different heterocyclic systems. Thus, their conversion to 1,3,5-triazines,[1-3] quinazolines,[2] triazoles[1] and oxadiazoles[1] have been reported. We now describe a new general synthetic method of the hitherto unknown 4,6-diaryl-2-cyanoiminopiperidines by reaction of *N*-cyanocinnamamidines **2** with different benzylidene compounds.

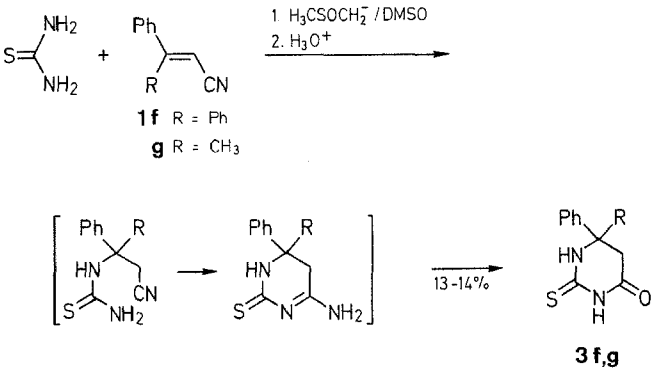
The *N*-cyanocinnamamidines **2** were prepared by stirring an equimolar mixture of the corresponding 3-arylpropenenitrile **1** and thiourea with 1 equivalent of sodium isopropoxide in isopropyl alcohol at room temperature (Table 1). The crude products, obtained according to isolation procedure, were contaminated only with the unreacted propenenitrile and purified by recrystallization.



1 **2**

The formation of the *N*-cyanocinnamamidines **2** can be explained by the addition of thiourea to the cyano group and subsequent loss of hydrogen sulfide or by a Michael two-step cycloaddition of thiourea followed by a base induced elimination.

Reactions of 3,3-diphenylpropenenitrile (**1f**) [or 3-methyl-3-phenylpropenenitrile (**1g**)] with thiourea under the same conditions as in the preceding cases did not lead to the corresponding *N*-cyanoamidines. By using dimsyl sodium in dimethyl sulfoxide, as basic medium, 4-oxo-2-thioxohexahydropyrimidines **3f, g** were obtained.



3f,g

Reaction of **2** with 3-aryl-2-cyanopropenamides **4** (or ethyl propenoates **5**) in the presence of sodium methoxide gave 4,6-diaryl-5-cyano-2-cyanoiminopiperidines **6** and **7**, respectively (Table 2).

Table 1. *N*-Cyanocinnamamidines **2** Prepared

Product	R	Yield (%)	mp (°C)	Molecular Formula[a]	IR (KBr) ν(cm^{-1})	^{1}H-NMR (DMSO-d_6/TMS) δ, J(Hz)	^{13}C-NMR (DMSO-d_6/TMS) δ
2a	Ph	30	208	$C_{10}H_9N_3$[b] (171.2)	3310, 3150, 2170, 1655	6.66 (d, 1H, J = 16, H-2); 7.13–7.88 (m, 6H, H-3 + H_{arom}); 8.34, 8.69 (2br s, 2H, NH_2)	116.90 (CN); 119.59 (C-2); 127.96, 129.04, 130.28 (C-2′ to C-6′); 134.18 (C-1′); 148.75 (C-3); 167.84 (C-1)
2b	4-$H_3CC_6H_4$	21	248–250	$C_{11}H_{11}N_3$ (185.2)	3360, 3200, 2170, 1660	2.30 (s, 3H, CH_3); 6.60 (d, 1H, J = 16.2, H-2); 7.21, 7.45 (A_2B_2, 4H, J_{AB} = 8.4); 7.59 (d, 1H, H-3); 8.05–8.89 (br, 2H, NH_2)	–
2c	4-$H_3COC_6H_4$	26	226–228	$C_{11}H_{11}N_3O$ (201.2)	3340, 3180, 2160, 1655	3.77 (s, 3H, OCH_3); 6.52 (d, 1H, J = 16.8, H-2); 7.01, 7.57 (A_2B_2, 4H, J_{AB} = 6.6); 7.64 (d, 1H, H-3); 7.94–8.80 (br, 2H, NH_2)	–
2d	4-ClC_6H_4	38	276–278	$C_{10}H_8ClN_3$ (205.6)	3350, 3190, 2180, 1670	6.65 (d, 1H, J = 15.6, H-2); 7.22–7.86 (m, 5H, H-3 + H_{arom}); 7.97–9.0 (br, 2H, NH_2)	–
2e	2-Furyl	21	196–197	$C_8H_7N_3O$[c] (161.2)	3360, 3200, 2180, 1655	6.46 (d, 1H, J = 15.6, H-2); 6.57 (br s, 1H_{arom}); 6.83 (br s, 1H_{arom}); 7.51 (d, 1H, H-3); 7.81 (br s, 1H_{arom}); 8.31, 8.63 (2br s, 2H, NH_2)	–

[a] Satisfactory microanalyses obtained: C ±0.37, H ±0.37, N ±0.32, Cl ±0.11 (Exceptions; **2b**: C −0.42, **2c**: C −0.44).

[b] MS: m/z (%) = 171 (M^+, 30); 170 (100); 153 (10); 143 (8); 128 (39).

[c] MS: m/z (%) = 161 (M^+, 100); 133 (92); 107 (44).

Table 2. 4,6-Diaryl-5-cyano-2-cyanoiminopiperidines **6** and **7** Prepared

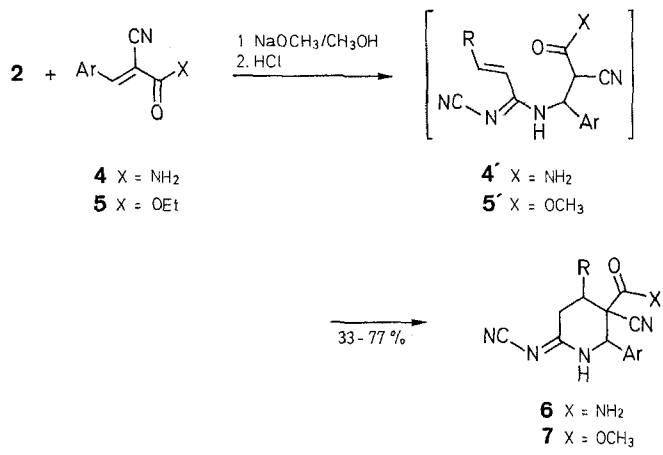
Product	Reaction Time (days)	Yield (%)	mp (°C)	Molecular Formula[a]	IR (KBr) ν (cm^{-1})	MS *m/z* (%)
6a	4	65	253–254	$C_{20}H_{17}N_5O$ (343.4)	3470, 3340, 2185, 1710, 1620	343 (M^+, 21); 299 (72); 186 (15); 171 (83); 104 (100)
6b	5	57	255–257	$C_{21}H_{19}N_5O$ (357.4)	3460, 3350, 2180, 1705, 1600	357 (M^+, 44); 314 (77); 186 (53); 171 (100); 119 (34)
6c	6	48	247–248	$C_{21}H_{19}N_5O_2$ (373.4)	3455, 3350, 2180, 1705, 1600	–
6d	6	50	200–202	$C_{20}H_{16}N_6O_3$ (388.4)	3470, 3350, 2180, 1705, 1600	–
6e	7	54	240–241	$C_{21}H_{19}N_5O$ (357.4)	3490, 3340, 2190, 1705, 1655, 1600	–
6f	7	70	236–237	$C_{21}H_{19}N_5O_2$ (373.4)	3410, 3330, 2190, 1700, 1600	–
6g	3	33	243–244	$C_{20}H_{16}ClN_5O$ (377.8)	3450, 3315, 2175, 1700, 1600	–
7a	4	77	212–213	$C_{21}H_{18}N_4O_2$ (358.4)	3220, 2190, 1740	358 (M^+, 6); 187 (48); 171 (100); 170 (100); 103 (40)
7b	4	75	203–205	$C_{22}H_{20}N_4O_2$ (372.4)	3220, 2180, 1745	372 (M^+, 23); 201 (8); 185 (73); 170 (100); 118 (23)
7c	6	62	194–195	$C_{22}H_{20}N_4O_3$ (388.4)	3220, 2180, 1740	–
7d	6	43	206–207	$C_{20}H_{17}N_5O_4$ (391.4)	3200, 2185, 1740	–
7e	3	49	189–191	$C_{22}H_{20}N_4O_2$ (372.4)	3200, 2200, 1750	–
7f	7	60	160–162	$C_{22}H_{20}N_4O_3$ (388.4)	3210, 2190, 1745	–
7g	1	73	148–150	$C_{21}H_{17}ClN_3O_2$ (378.8)	3220, 2200, 1750	–

[a] Satisfactory microanalyses obtained: C ±0.38, H ±0.29, N ±0.45, Cl ±0.33 (Exceptions; **6a**: N −0.45, **7f**: N −0.45).

Table 3. ^{1}H- and ^{13}C-NMR Data of Compounds **6**, **7** and **12**

Product	^{1}H-NMR (DMSO-d_6/TMS) δ, J(Hz)	^{13}C-NMR (DMSO-d_6/TMS) δ
6a	3.02–3.39 (m, 2H, H-3); 3.39–4.04 (m, 1H, H-4); 5.27 (s, 1H, H-6); 7.35 (s, 12H, H_{arom} + $CONH_2$); 9.81 (br s, 1H, NH)	33.13[a] (C-3); 42.58[a] (C-4); 58.09 (C-5); 61.33[a] (C-6); 116.10, 116.59 (CN); 127.71, 127.95, 128.35, 128.50, 128.75, 129.40 (C-2′ to C-6′); 134.84, 136.64 (C-1′); 164.49 ($CONH_2$); 172.64 (C-2)
6b	2.29 (s, 3H); 2.94–3.31 (m, 2H, H-3); 3.75–4.13 (m, 1H, H-4); 5.22 (s, 1H, H-6); 6.99–7.55 (m, 11H, H_{arom} + $CONH_2$); 9.73 (br s, 1H, NH)	–
6c	3.0–3.44 (m, 2H, H-3); 3.73 (s, 3H, OCH_3); 3.81–4.19 (m, 1H, H-4); 5.21 (s, 1H, H-6); 6.75–7.63 (m, 11H, H_{arom} + $CONH_2$); 9.75 (br s, 1H, NH)	–
6d	3.03–3.47 (m, 2H, H-3); 3.91–4.31 (m, 1H, H-4); 5.43 (s, 1H, H-6); 7.35 (s, 7H, H_{arom} + $CONH_2$); 7.57, 8.27 (A_2B_2, 4H, J_{AB} = 8); 9.96 (br s, 1H, NH)	–
6e	2.23 (s, 3H, CH_3); 3.03–3.47 (m, 2H, H-3); 3.73–4.27 (m, 1H, H-4); 5.27 (s, 1H, H-6); 6.93–7.63 (m, 11H, H_{arom} + $CONH_2$); 9.80 (br s, 1H, NH)	–
6f	2.97–3.47 (m, 2H, H-3); 3.70 (s, 3H, OCH_3); 3.80–4.19 (m, 1H, H-4); 5.21 (s, 1H, H-6); 6.89, 7.33 (A_2B_2, 4H, J_{AB} = 10.2); 7.36 (s, 7H, H_{arom} + $CONH_2$); 9.80 (br s, 1H, NH)	–
6g	3.0–3.50 (m, 2H, H-3); 3.83–4.37 (m, 1H, H-4); 5.30 (s, 1H, H-6); 7.10–7.73 (m, 11H, H_{arom} + $CONH_2$); 9.83 (br s, 1H, NH)	–
7a	3.37 (s, 3H, CO_2CH_3); 3.12–3.50 (m, 2H, H-3); 3.94–4.38 (m, 1H, H-4); 5.29 (s, 1H, H-6); 7.34 (s, 10H_{arom}); 9.89 (br s, 1H, NH)	32.35[a] (C-3); 43.22[a] (C-4); 53.63 ($CO_2\underline{C}H_3$); 58.43 (C-5); 61.39[a] (C-6); 114.55, 116.45 (CN); 127.56, 127.72, 127.96, 128.78, 128.90, 129.76 (C-2′ to C-6′); 134.26, 135.84 (C-1′); 165.25 ($\underline{C}O_2CH_3$); 172.74 (C-2)
7b	2.29 (s, 3H, CH_3); 2.94–3.56 (m, 2H, H-3); 3.36 (s, 3H, CO_2CH_3); 3.81–4.31 (m, 1H, H-4); 5.25 (s, 1H, H-6); 7.17 (s, 4H_{arom}); 7.34 (s, 5H_{arom}); 9.86 (br s, 1H, NH)	–
7c	3.06–3.44 (m, 2H, H-3); 3.37 (s, 3H, CO_2CH_3); 3.74 (s, 3H, OCH_3); 3.88–4.31 (m, 1H, H-4); 5.24 (s, 1H, H-6); 6.97, 7.19 (A_2B_2, 4H, J_{AB} = 8.8); 7.34 (s, 5H_{arom}); 9.86 (br s, 1H, NH)	–
7d	3.06–3.56 (m, 2H, H-3); 3.48 (s, 3H, CO_2CH_3); 4.0–4.38 (m, 1H, H-4); 5.52 (s, 1H, H-6); 7.36 (s, 5H_{arom}); 7.56, 8.28 (A_2B_2, 4H, J_{AB} = 8); 10.08 (br s, 1H, NH)	–
7e	2.27 (s, 3H, CH_3); 3.06–3.53 (m, 2H, H-3); 3.40 (s, 3H, CO_2CH_3); 3.86–4.43 (m, 1H, H-4); 5.33 (s, 1H, H-6); 7.23 (s, 4H_{arom}); 7.40 (s, 5H_{arom}); 9.97 (br s, 1H, NH)	–
7f	3.07–3.57 (m, 2H, H-3); 3.47 (s, 3H, CO_2CH_3); 3.77 (s, 3H, OCH_3); 3.90–4.37 (m, 1H, H-4); 5.28 (s, 1H, H-6); 6.97, 7.33 (A_2B_2, 4H, J_{AB} = 8.4); 7.40 (s, 5H_{arom}); 9.97 (br s, 1H, NH)	–
7g	3.10–3.56 (m, 2H, H-3); 3.43 (s, 3H, CO_2CH_3); 3.83–4.33 (m, 1H, H-4); 5.33 (s, 1H, H-6); 7.39 (s, 4H_{arom}); 7.43 (s, 5H_{arom}); 9.90 (br s, 1H, NH)	–
12	4.38 (AB syst., 1H, J_{AB} = 13.2, H-4); 4.90 (AB syst., 1H, J = 13.2, H-3); 5.33 (s, 1H, H-6); 7.36 (s, 12H_{arom} + $CONH_2$); 8.86 (br s, 1H, NH)	38.68[a] (C-3); 46.35[a] (C-4); 58.40 (C-5); 60.28[a] (C-6); 115.29, 116.63 (CN); 127.70, 127.95, 128.20, 128.57, 129.05 (C-2′ to C-6′); 134.39, 134.98 (C-1′); 162.81, 163.73 (C-2 + $CONH_2$)

[a] Splitting in „off resonance" spectrum.



4 X = NH_2
5 X = OEt

4′ X = NH_2
5′ X = OCH_3

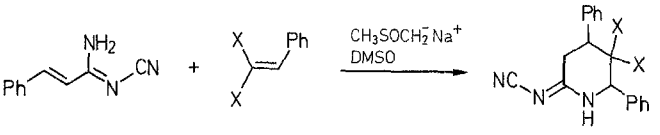
33–77 %

6 X = NH_2
7 X = OCH_3

6, 7	R	Ar	6, 7	R	Ar
a	Ph	Ph	**e**	4-$H_3CC_6H_4$	Ph
b	Ph	4-$H_3CC_6H_4$	**f**	4-$H_3COC_6H_4$	Ph
c	Ph	4-$H_3COC_6H_4$	**g**	4-ClC_6H_4	Ph
d	Ph	4-$O_2NC_6H_4$			

Although an investigation of the reaction mechanism was not undertaken, the reaction pathway is considered to proceed by addition of the *N*-cyanocinnamamidine **2** to the benzylidene compounds **4** and **5**. The resulting adduct **4′**/**5′** undergoes *in situ* cyclization to give the 2-cyanoiminopiperidines **6** and **7**, respectively.

Similarly, the reactions of 2-cyano-3-phenylpropenenitrile **(8)** and ethyl 2-ethoxycarbonyl-3-phenylpropenoate **(9)** with the *N*-cyanocinnamamidine **(2a)** in dimethyl sulfoxide at room temperature in the presence of one equivalent of dimsyl sodium afford the 4,6-diphenyl-2-cyanoiminopiperidines **10** and **11**, respectively.

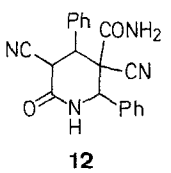


2a

8 X = CN
9 X = CO_2Et

10 X = CN (23%)
11 X = CO_2Et (56%)

The structure of the 2-cyanoiminopiperidines **6, 7, 10** and **11** was established on the basis of spectroscopic data. The unequivocal assignement of the ^1H- and ^{13}C-NMR spectra was carried out by comparison with the corresponding spectrum of the 5-carbamoyl-3,5-dicyano-4,6-diphenyl-2-piperidone **(12)**.



12

Melting points were determined on a Electrothermal IA 6304 apparatus and are uncorrected. Mass spectra were recorded on a Varian MAT 711 instrument. IR spectra were recorded on a Perkin-Elmer 1310 spectrophotometer. ^1H-NMR spectra were obtained on a WP Bruker 60 WC and on a Varian FT-80 A spectrometers. ^{13}C-NMR spectra were recorded on a Varian FT-80 A spectrometer.

(*E*)-3-Phenylpropenenitrile **(1a)** was purchased from Aldrich and used without further purification. (*E*)-3-Arylpropenenitriles **1b–g** were prepared according to the reported procedure.[4] 5-Carbamoyl-3,5-dicyano-4,6-diphenyl-2-piperidone **(12)** was obtained by the literature procedure.[5]

(*E*)-*N*-Cyanocinnamamidines 2a–e; General Procedure:
A solution of sodium isopropoxide (1.64 g, 20 mmol), thiourea (1.52 g, 20 mmol) and the corresponding (*E*)-3-arylpropenenitrile **1a–e** (20 mmol) in dry isopropyl alcohol (65 mL) is stirred at room temperature for 10 days and then the solvent is removed *in vacuo*. By addition of EtOH (10 mL) and water (200 mL), a precipitate is formed which is collected and washed with water and ether. The crude product is recrystallized from EtOH to afford the (*E*)-*N*-cyanocinnamamidines **2a–e** (Table 1).

4-Oxo-6,6-diphenyl-2-thioxohexahydropyrimidine (3f):
To a suspension of dimsyl sodium in DMSO (20 mL; prepared using 25 mmol of NaH), thiourea (1.52 g, 20 mmol) and 3,3-diphenylpropenenitrile (**1f**; 4.1 g, 20 mmol) are added. The mixture is stirred at room temperature for 10 days and then poured into water (100 mL). The precipitate thus obtained is identified (IR spectrum) with the starting propenenitrile. The combined mother liquor is acidified with CF_3CO_2H (3 mL) and the resulting white precipitate is filtered and recrystallized from MeCN; yield: 730 mg (13%); mp 280–281 °C.

$C_{16}H_{14}N_2OS$ calc. C 68.06 H 5.00 N 9.92 S 11.36
(282.3) found 67.82 5.15 9.58 11.71

IR (KBr): ν = 3150, 1705, 1560, 1495, 1450, 1315 cm^{-1}.

^1H-NMR (DMSO-d_6): δ = 3.4 (s, 2H, H-5); 7.35 (s, 10 H_{arom}); 10.53 (s, 1H, NH-1); 10.92–11.32 (br s, 1H, NH-3).

6-Methyl-4-oxo-6-phenyl-2-thioxohexahydropyrimidine (3g):
Thiourea (1.52 g, 20 mmol) and 3-methyl-3-phenylpropenenitrile (**1g**; *E*/*Z* = 5.7; 2.86 g, 20 mmol) are added to a suspension of dimsyl sodium in DMSO (20 mL; prepared using 25 mmol of NaH). The mixture is maintained with stirring at room temperature for 10 days, then poured into water (100 mL) and acidified with 10% HCl (10 mL). The solid formed is separated by filtration and recrystallized from MeCN; yield: 620 mg (14%); mp 233–235 °C.

$C_{11}H_{12}N_2OS$ calc. C 59.97 H 5.49 N 12.72 S 14.56
(220.3) found 59.72 5.63 12.60 14.71

IR (KBr): ν = 3160, 1705, 1560, 1495, 1445, 1315 cm^{-1}.

^1H-NMR (DMSO-d_6): δ = 1.52 (s, 3H, CH_3); 3.05 (s, 2H, H-5); 7.37 (s, 5 H_{arom}); 10.27 (s, 1H, NH-1); 11.0 (s, 1H, NH-3).

4,6-Diaryl-5-cyano-2-cyanoiminopiperidines 6 and 7; General Procedure:
To a solution of sodium (23 mg, 1 mmol) in dry MeOH (40 mL), the corresponding (*E*)-*N*-cyanocinnamamidine **2** (1 mmol) and the 3-aryl-2-cyanopropenamide **4** (or ethyl 3-aryl-2-cyanopropenoate **5**) (1 mmol) are added. After stirring at room temperature (Table 2) the mixture is concentrated to one third of the initial volume, poured into water (50 mL) and acidified with 2% HCl (10 mL). The precipitate is collected, washed with water and recrystallized from EtOH in all cases.

5,5-Dicyano-2-cyanoimino-4,6-diphenylpiperidine (10):
To a suspension of sodium methylsulfinylmethanide in DMSO (5 mL; prepared using 2.3 mmol of sodium hydride), (*E*)-*N*-cyanocinnamamidine (**2a**; 342 mg, 2 mmol) and 2-cyano-3-phenylpropenenitrile (**8**, 308 mg, 2 mmol) are added. The mixture is stirred at room temperature for 9 days and then poured into water (100 mL) and acidified with 2% HCl (15 mL). The precipitate thus obtained is collected and recrystallized from EtOH; yield: 149 mg (23%); mp 192–194 °C.

$C_{20}H_{15}N_5$ calc. C 73.83 H 4.65 N 21.53
(325.4) found 73.70 4.61 21.97

IR (KBr): ν = 3320, 2190, 1610 cm^{-1}.

^1H-NMR (DMSO-d_6): δ = 3.09–3.60 (m, 2H, H-3); 4.05–4.50 (m, 1H, H-4); 5.56 (s, 1H, H-6); 7.49 (s, 10 H_{arom}); 10.06 (br s, 1H, NH).

MS (70 eV): *m*/*z* (%) = 325 (M^+, 21); 171 (100); 170 (72); 104 (80).

2-Cyanoimino-5,5-diethoxycarbonyl-4,6-diphenylpiperidine (11):
To a suspension of dimsyl sodium in DMSO (5 mL, prepared using 2.5 mmol of NaH), (*E*)-*N*-cyanocinnamamidine (**2a**; 342 mg, 2 mmol) and ethyl 2-ethoxycarbonyl-3-phenylpropenoate (**9**, 496 mg, 2 mmol) are added. After stirring at room temperature for 4 days the mixture is poured into water (100 mL) and acidified with 10% HCl (5 mL). The solid thus obtained is chromatographed on a silica gel column using hexane/EtOAc (8:2) as eluent affording a white solid that is recrystallized from ethanol; yield: 430 mg (56%); mp 184–186 °C.

$C_{24}H_{25}N_3O_4$ calc. C 68.71 H 6.01 N 10.02
(419.5) found 68.80 5.94 10.19

IR (KBr): ν = 3310, 2190, 1755, 1725, 1615 cm^{-1}.

^{1}H-NMR (DMSO-d_6): $\delta = 0.70-1.33$ (m, 6H, CH_2CH_3); 2.63–4.43 (m, 7H, H-3, H-4, CH_2CH_3): 5.24 (s, 1H, H-6); 7.27 (s, $5H_{arom}$); 7.37 (s, $5H_{arom}$); 9.77 (br s, 1H, NH).

MS (70 eV): m/z (%) = 419 (M^+, 41); 346 (100); 300 (73); 272 (14); 249 (18); 171 (73); 170 (91); 104 (64).

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