An Efficient Preparation of New Homoallylamines and α-Aminonitriles Bearing Furyl and Thienyl Rings

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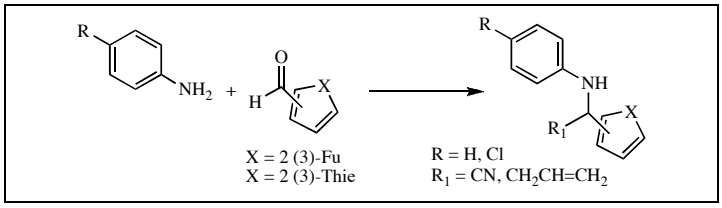

New diverse *N*-aryl-*N*-[1-furyl(thienyl)but-3-enyl]amines (homoallylamines) or 2-(*N*-arylmethylamino)-2-furyl(thienyl)acetonitriles (α-aminonitriles) were easily prepared in good to excellent yields by an indium-mediated Barbier-type reaction between *N*-hetarylaldimines and allyl bromide in MeOH or a direct three component reaction between anilines, hetaryl aldehydes and trimethylsilyl cyanide in the presence of a catalytic amount of molecular iodine at room temperature, respectively. The entire set of amines was characterized by IR, ^{1}H and ^{13}C NMR spectroscopy.

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INTRODUCTION

N-Substituted but-3-enylamines, - homoallylamines, are an important and interesting class of organic molecules, which have been always the focus of attention for organic, bioorganic and medicinal chemists due to their many synthetic applications [1,2] as well as their biological properties [3-5]. α-Aminonitriles are also important intermediates for several amino acids as well as for popular bifunctional synthons that have found numerous synthetic applications [6]. Both these substructures are usually prepared from azomethines *via* nucleophilic addition reactions such as the Grignard-Barbier allylations [7-10] and Strecker-type reactions [11-16]. The respective allyl or cyanide ion addition reactions provide an access to new drug-like molecules by introducing a stereogenic center and a carbon-carbon bond in one step. So, allylation and cyanation reactions are important reactions in synthetic organic chemistry and medicinal chemistry. Moreover, oxygen and sulfur heterocycles are frequently found in privileged structures (pharmacophores); among them, furan and thiophene derivatives represent good candidates for bioscreening of diverse types of activities.

With these fact in mind and as a development of our medicinal program directed to small molecules for drug delivery, we were particularly interested in diverse *N*-aryl-*N*-[1-furyl(thienyl)but-3-enyl]amines (homoallylamines) or (2-(*N*-arylmethylamino)-2-furyl(thienyl) acetonitriles (α-aminonitriles) that could serve as useful precursors to many drug-like molecules and interesting biological models in our quest for compounds with antifungal and antiparasitic properties [3-5]. The results of our investigation on synthesis and spectral characterization of this type of molecules are reported in this paper.

RESULTS AND DISCUSSION

In our quest for new homoallylamines and related compounds with antifungal and antiparasitic properties, we exploited with some success Grignard reaction between imines and preformed allylmagnesium bromide in dry bipolar aprotic solvents (Et_2O, THF, *etc*) [3-5]. However, there are still limitations in these reactions: first, the scope of application to imines is still narrow because of their stability; second, imines are less reactive compared with the corresponding carbonyl compounds because of their low electrophilicity, which makes it difficult to realize a one-pot sequential version of the Grignard multicomponente reaction.

To prepare new diverse *N*-aryl-*N*-[1-furyl(thienyl)but-3-enyl]amines, now we employed the Barbier-type reaction, when the organometallic reagent has low reactivity toward water or alcoholic solvents and is formed in the reaction mediated by mixing the metal, halide and electrophilic substrate in a one-pot reaction.

The *N*-furylaldimines **1** and *N*-thienylaldimines **2**, the main starting materials in our research on this allylation reaction, were easily prepared from commercially available 2-(3)-furancarboxyaldehydes or 2-(3)-thiophencarboxyaldehydes and substituted anilines, according to published methods [17,18]. Reactions of aldimines **1,2** with the allyl indium reagent generated *in situ* by addition of allyl bromide to a suspension of indium powder were realized in dry MeOH (Scheme I).

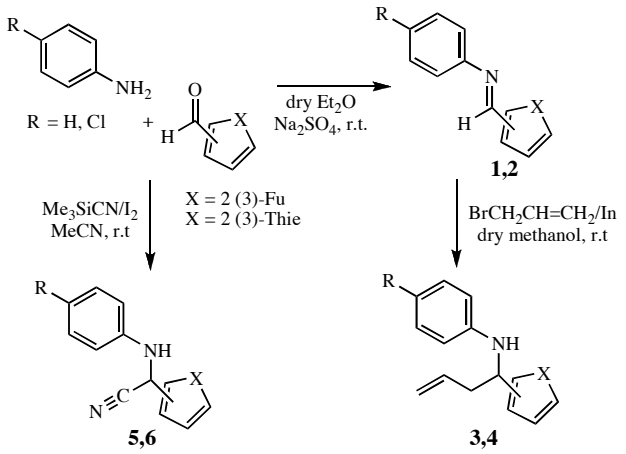
After a standard work-up, this reaction furnished the desired homoallylic amines **3** and **4** as viscous oils in

good to excellent yields (Table 1). The products were purified by chromatography on a short silica gel column. In the ^{1}H nmr spectra of the amines **3** and **4**, the protons of the butene chain gave rise to very characteristic groups of signals. The triplet (J = 6.2-6.3 Hz) from a proton at C-4 was observed in the region δ 4.39-4.60 ppm. A signal for two protons corresponding to the group 3-CH_2 appeared in the region δ 2.60-2.66 ppm. The two multiplets between δ 5.26-5.17 and δ 5.94-5.70 ppm are due to the olefinic hydrogens, –CH_2= and –CH=, respectively. The ir spectra of homoallylamines **3,4** showed a characteristic band for the amino group in the region of 3415-3410 and 1605-1601 cm^{-1}.

The mass spectra of these compounds contain low-intensity (< 1-5%) molecular ion peaks which agree with the expected molecular mass. The maximum peaks belong to the fragmentation (M-C_3H_5)$^{+\cdot}$.

So, new homoallylamines bearing furyl or thienyl rings were easily obtained using an allyl bromide-indium-methanol system at room temperature that could be utilized in multi-component Grignard-type reactions and avoids the use of anhydrous ether.

Scheme I



Second part of our research was the preparation of new 2-(*N*-arylmethylamino)-2-furyl(thienyl)aceto-nitriles (**5,6**) that could be considered as amine analogues of prepared compounds **3,4**. In comparison with the homoallylamines preparation, their synthesis can be easily performed *via* three-component condensation of heteroaldehydes, anilines and either hydrogen cyanide or its alkaline metal cyanides. Although catalyst-free three-component Strecker reaction in acetonitrile was reported [14], we considered that I_2-catalyzed three-component coupling of chosen aldehydes and anilines in the presence of trimethylsilyl cyanide (TMSCN) [13] would be appropriated to generate new α-amino nitriles needed in our future pharmacological investigation.

Thus, the treatment of the same aldehydes and anilines with TMSCN in the presence of a catalytic amount of iodine in MeCN at room temperature afforded 2-(*N*-arylmethylamino)-2-furyl(thienyl)aceto-nitriles (**5,6**) in good to excellent yields (Scheme 1, Table 1). The obtained α-aminonitriles showed in the ir spectra the characteristic NH and CN bands appearing in the region of 3367-3356 and 2241-2237 cm^{-1}, respectively. Their structures were also consistent with their ^{1}H- and ^{13}C-nmr spectra and supported by the mass spectrometric data. In the ^{1}H nmr spectra of the α-aminonitriles **5,6**, the aliphatic proton H-2 resonates between 5.50 and 5.28 ppm as a singlet (comp. **5a,b** and **6b**) or as a doublet (J = 8.1-8.8 Hz) (comp. **6a,c**), due to the interaction with NH group.

So, new 2-hetarylacetonitriles (**5,6**) were easily obtained using a simple one-pot procedure where iodine acts efficiently as a mild Lewis acid that could be a useful and inexpensive catalyst for the generation of α-aminonitriles based on heteroaldehydes.

In summary, two series of new potentially bioactive secondary amines were prepared. The import features of the used methods include a) operational simplicity, b) good yields of the desired amines, c) short reaction times. All products **3-6** were evaluated as possible antifungal agents. These compounds possess from moderate to good antifungal activity against certain type of fungi (hialohyphomycetes or dermatophytes) [19].

Table 1

Comp.	R	X	Molecular Formula	M.W. (g/mol)	MS (M$^{+\cdot}$, m/z)	Yield (%)	IR (ν, cm^{-1})
3a	H	3-O	$C_{14}H_{15}NO$	213.28	213 (M$^+$), 172 [(M-C_3H_5)$^+$]	95	3410, 1601, 1504, 922
3b	Cl	3-O	$C_{14}H_{14}ClNO$	247.72	247 (M$^+$), 206 [(M-C_3H_5)$^+$ for ^{35}Cl]	57	3413, 1601, 1497, 922
4a	H	2-S	$C_{14}H_{15}NS$	229.34	229 (M$^+$), 188 [(M-C_3H_5)$^+$]	88	3405, 1609, 1498, 920
4b	Cl	2-S	$C_{14}H_{14}ClNS$	263.79	263 (M$^+$), 222 [(M-C_3H_5)$^+$ for ^{35}Cl]	57	3413, 1595, 1497, 923
4c	H	3-S	$C_{14}H_{15}NS$	229.34	229 (M$^+$), 188 [(M-C_3H_5)$^+$]	97	3410, 1601, 1504, 918
4d	Cl	3-S	$C_{14}H_{14}ClNS$	263.79	263 (M$^+$), 222 [(M-C_3H_5)$^+$ for ^{35}Cl]	48	3413, 1597, 1497, 922
5a	H	2-O	$C_{12}H_{10}N_2O$	198.22	198 (M$^+$)	61	3359, 2241, 1605
5b	H	3-O	$C_{12}H_{10}N_2O$	198.22	198 (M$^+$)	62	3356, 2237, 1605
6a	H	2-S	$C_{12}H_{10}N_2S$	214.29	214 (M$^+$)	80	3356, 2237, 1605
6b	H	3-S	$C_{12}H_{10}N_2S$	214.29	214 (M$^+$)	84	3367, 2237, 1601
6c	Cl	3-S	$C_{13}H_{12}ClN_2S$	248.73	248 (M$^+$)	88	3356, 2237, 1601

EXPERIMENTAL

Melting points were uncorrected and measured in a FISHER-JOHNS melting point apparatus. Infrared spectra were recorded on an Infralum (Lumex) FT-IR spectrometer as KBr pellets or neat. The ^{1}H and ^{13}C nmr spectra were determined on Bruker AM-300, in deuterium chloroform with tetramethylsilane as internal standard. Data are reported as follows: chemical shifts (multiplicity, number of protons, coupling constants and group). On dept-135 spectra, the signals of CH_3, CH_2 and CH carbons are shown as positive (+) and negative (-), respectively. Quaternary carbons are not shown. Mass spectra were recorded with a HP 5890 A Series II, link to a network Mass selective detector HP 5972, a spectrometer with 70 eV electron impact ionization. The purities of the obtained substance were monitoring by thin layer chromatography on Silufol UV_{254} sheets. Elemental analyses were performed on a Leco CHN-600 analyzer. Solvents and common reagents obtained from Merck and Aldrich were reagent grade.

General procedure for the synthesis of *N*-aryl-*N*-[1-furyl(thienyl)but-3-enyl]amines (3,4). To a mixture of the aldimine **1,2** (2.2 mmol) and indium powder (375 mg, 3.3 mmol) in absolute methanol (10 mL) was added allyl bromide (800 mg, 0.590 mL, 6.6 mmol). The reaction was stirred vigorously at room temperature until all the indium had dissolved (1 h to 4 h), at which time TLC indicated complete reaction. The reaction mixture was diluted with sat. NH_4Cl and extracted with ethyl acetate. The extract was washed with brine and dried (Na_2SO_4). The product was purified by flash column chromatography on silica gel, using hexanes/ethyl acetate as eluent. Physicochemical characteristics of the synthesized homoallylamines **3,4** are given in the Table 1.

***N*-Phenyl-*N*-[1-(3-furyl)but-3-enyl]amine (3a).** The compound **3a** was obtained in 95 % yield, red oil. ir (potassium bromide): ν = 3410, 1601, 1504, 922 cm^{-1}. ^{1}H nmr (deuterium chloroform): δ 7.43 (1H, t, J = 1.7 Hz, 5-H_{Fu}), 7.39 (1H, s, 2-H_{Fu}), 7.20 (2H, t, J = 7.5, Hz, 3(5)-H_{Ph}), 6.76 (1H, t, J = 7.3 Hz, 4-H_{Ph}), 6.66 (1H, d, J = 7.9 Hz, 2(6)-H_{Ph}), 6.42 (1H, br.s, 4-H_{Fu}), 5.94-5.79 (1H, m, =CH), 5.26-5.17 (2H, m, CH_2=), 4.50 (1H, t, J = 6.3 Hz, 4-H), 2.63 (2H, t, J = 6.8 Hz, -CH_2), ^{13}C nmr (75 MHz): δ 147.2, 143.1 (+), 139.5 (+), 134.3 (+), 129.1 (2C, +), 127.7, 118.3 (-), 117.6 (+), 113.5 (2C, +), 109.0 (+), 49.4 (+), 41.0 (-). ms: m/z: 213 (molecular ion), 172 [(M-C_3H_5)$^+$].

Anal. Calcd. for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.66; H, 7.16; N, 6.50.

***N*-(4-Chlorophenyl)-*N*-[1-(3-furyl)but-3-enyl]amine (3b).** The compound **3b** was obtained in 57 % yield, red oil. ^{1}H nmr (deuterium chloroform): δ 7.38 (1H, t, J = 1.6 Hz, 5-H_{Fu}), 7.32 (1H, br.d, J = 0.6 Hz, 2-H_{Fu}), 7.09 (2H, d, J = 8.8, Hz, 3(5)-H_{Ar}), 6.52 (2H, d, J = 8.8 Hz, 2(6)-H_{Ar}), 6.35 (1H, br.t, J = 0.7 Hz, 4-H_{Fu}), 5.85-5.71 (1H, m, =CH), 5.21-5.14 (2H, m, CH_2=), 4.39 (1H, t, *J* = 6.2 Hz, 4-H), 2.56 (2H, td, J = 6.9, 1.4 Hz, -CH_2). ^{13}C nmr (75 MHz): δ 145.8, 143.3 (+), 139.5 (+), 134.0 (+), 128.9 (2C, +), 127.3, 121.1, 118.5 (-), 114.6 (2C, +), 108.9 (+), 49.5 (+), 41.0 (-). ms: m/z: 247 (molecular ion), 206 [(M-C_3H_5)$^+$ for ^{35}Cl]. *Anal.* Calcd. for $C_{14}H_{14}ClNO$: C, 67.88; H, 5.70; N, 5.65. Found: C, 67.75; H, 5.91; N, 5.48.

***N*-Phenyl-*N*-[1-(2-thienyl)but-3-enyl]amine (4a).** The compound **4a** was obtained in 88% yield, yellow oil. Its spectral data were in agreement with those reported in literature [5].

***N*-(4-Chlorophenyl)-*N*-[1-(2-thienyl)but-3-enyl]amine (4b).** The compound **4b** was obtained in 57 % yield, yellow oil. ^{1}H nmr (deuterium chloroform): δ 7.10 (1H, dd, *J* = 4.5, 1.6 Hz, 5-H_{Thie}), 6.99 (2H, d, *J* = 8.6 Hz, 3(5)-H_{Ar}), 6.88-6.85 (2H, m, 3(4)-H_{Thie}), 6.44 (2H, d, *J* = 8.6 Hz, 2(6)-H_{Ar}), 5.78-5.64 (1H, m, =CH), 5.14-5.08 (2H, m, CH_2=), 4.58 (1H, t, *J* = 6.6 Hz, 4-H), 4.20 (1H, br.d, H-N), 2.61-2.55 (2H, m, -CH_2), ^{13}C nmr (75 MHz): δ 147.9, 145.4, 133.7 (+), 129.0 (2C, +), 126.8 (+), 123.9 (+), 123.7 (+), 122.7, 118.9 (-), 114.9 (2C, +), 53.6 (+), 43.0 (-). ms: m/z: 263 (molecular ion), 222 [(M-C_3H_5)$^+$ for ^{35}Cl]. *Anal.* Calcd. for $C_{14}H_{14}ClNS$: C, 63.74; H, 5.35; N, 5.31. Found: C, 63.96; H, 5.56; N, 5.20.

***N*-Phenyl-*N*-[1-(3-thienyl)but-3-enyl]amine (4c).** The compound **4c** was obtained in 97% yield, yellow oil. ^{1}H nmr (deuterium chloroform): δ 7.34 (1H, dd, J = 4.9, 3.0 Hz, 5-H_{Thie}), 7.20-7.15 (3H, m, 3(5)-H_{Ph}, and 2-H_{Thie}), 7.11 (1H, dd, J = 5.0, 1.2 Hz, 4-H_{Thie}), 6.74 (1H, t, J = 7.3 H, 4-H_{Ph}), 6.62 (2H, d, J = 7.7 Hz, 2(6)-H_{Ph}), 5.92-5.75 (1H, m, =CH), 5.26-5.18 (2H, m, CH_2=), 4.60 (1H, t, J = 6.5 Hz, 4-H), 2.67 (2H, q, J = 6.7 Hz, -CH_2), ^{13}C nmr (75 MHz): δ 147.2, 144.7, 134.4 (+), 129.1 (2C, +), 127.7, 126.1 (+), 126.0 (+), 120.8 (+), 118.3 (-), 117.6 (+), 113.6 (+), 53.4 (+), 41.9 (-). ms: m/z: 229 (molecular ion), 188 [(M-C_3H_5)$^+$]. *Anal.* Calcd. for $C_{14}H_{15}NS$: C, 73.32; H, 6.59; N, 6.11. Found: C, 73.50; H, 6.45; N, 6.24.

***N*-(4-Chlorophenyl)-*N*-[1-(3-thienyl)but-3-enyl]amine (4d).** The compound **4b** was obtained in 48 % yield, yellow oil. ^{1}H nmr (deuterium chloroform): δ 7.29 (1H, dd, J = 4.9, 3.0 Hz, 5-H_{Thie}), 7.12 (1H, br.d, J = 2.9 Hz, 2-H_{Thie}), 7.06 (2H, d, J = 8.8 Hz, 3(5)-H_{Ar}), 7.04 (1H, dd, J = 5.3, 1.0 Hz, 4-H_{Thie}), 6.48 (2H, d, J = 8.7 Hz, 2(6)-H_{Ar}), 5.84-5.65 (1H, m, =CH), 5.21-5.14 (2H, m, CH_2=), 4.50 (1H, t, J = 6.5 Hz, 4-H), 2.69-2.52 (2H, m, -CH_2), ^{13}C nmr (75 MHz): δ 145.7, 144.2, 134.1 (+), 128.9 (2C, +), 126.2 (+), 125.9 (+), 122.2, 120.9 (+), 118.5 (-), 114.6 (2C, +), 53.5 (+), 41.8 (-). ms: m/z: 263 (molecular ion), 222 [(M-C_3H_5)$^+$ for ^{35}Cl]. *Anal.* Calcd. for $C_{14}H_{14}ClNS$: C, 63.74; H, 5.35; N, 5.31. Found: C, 63.87; H, 5.55; N, 5.57.

General procedure for the synthesis of 2-(*N*-arylmethyl-amino)-2-furyl(thienyl)acetonitriles (5,6). To a mixture of heteroaldehyde (5.4 mmol), anilines (5.4 mmol), and TSCN (0.535 mg, 5.4 mmol) in dry MeCN (8 mL) was stirred at room temperature for 20-30 min. To the reaction mixture was added the iodine (140 mg, 0.54 mmol). After completion of reaction (1-3h, TLC), the colored reaction mixture was diluted with sat. NH_4Cl (30 mL) and extracted with ethyl acetate. The extract was washed with brine and dried (Na_2SO_4). The product was purified by flash column chromatography on silica gel, using hexanes/ ethyl acetate as eluent. Physicochemical characteristics of the synthesized α-aminonitriles **5,6** are given in the Table 1.

2-(2-Furyl)-2-(phenylamino)acetonitrile (5a). The compound **5a** was obtained in 61 % yield, red oil. Its spectral data were in agreement with those reported in literature [12].

2-(3-Furyl)-2-(phenylamino)acetonitrile (5b). The compound **5b** was obtained in 62 % yield, red oil. ^{1}H nmr (deuterium chloroform): δ 7.62 (1H, s, J = 0.9 Hz, 5-H_{Fu}), 7.41 (2H, br.t, J = 1.4 Hz, 2-H_{Fu}), 7.21 (2H, t, J = 7.6 Hz, 3(5)-H_{Ph}), 6.84 (1H, t, J = 7.4 Hz, 4-H_{Ph}), 6.70 (2H, d, J = 7.8 Hz, 2(6)-H_{Ph}), 6.47 (1H, s, 4-H_{Fu}), 5.27 (1H, s, HC-CN), 3.92 (1H, br.s, H-N), ^{13}C nmr (75 MHz): δ 144.5 (+), 144.3, 141.0 (+), 129.6 (2C, +), 120.5 (+), 120.1, 117.8, 114.3 (2C, +), 109.1 (+), 42.5 (+). ms: m/z: 198 (molecular ion). *Anal.* Calcd. for $C_{15}H_{12}N_2O$: C, 72.71; H, 5.08; N, 14.13. Found: C, 72.66; H, 5.26; N, 14.20.

2-(Phenylamino)-2-(2-thienyl)acetonitrile (6a). The compound **6a** was obtained in 80% yield, yellow oil. ^{1}H nmr (deuterium chloroform): δ 7.26-7.23 (2H, m, 3,5-H_{Thie}), 7.16

(2H, t, J = 7.7 Hz, 3(5)-H_{Ph}), 6.92 (1H, t, J = 4.1 Hz, 4-H_{Thie}), 6.81 (1H, t, J = 7.3 Hz, 4-H_{Ph}), 6.67 (2H, d, J = 8.4 Hz, 2(6)-H_{Ph}), 5.50 (1H, d, J = 8.1 Hz, HC-CN), 4.12 (1H, br.d, J = 8.3 Hz, H-N), ^{13}C nmr (100 MHz): δ 144.0, 136.7, 129.5 (+), 127.1 (2C, +), 127.0 (2C, +), 120.6 (+), 117.5, 114.5 (2C, +), 46.0 (+). ms: m/z: 214 (molecular ion). *Anal*. Calcd. for $C_{12}H_{10}N_2S$: C, 67.26; H, 4.70; N, 13.07. Found: C, 67.38; H, 4.46; N, 13.33.

2-(Phenylamino)-2-(3-thienyl)acetonitrile (6b). The compound **6b** was obtained in 84 % yield, yellow oil. ^{1}H nmr (deuterium chloroform): δ 7.42 (1H, t, J = 1.4 Hz, 2-H_{Thie}), 7.26 (1H, dd, J = 5.0, 3.0 Hz, 5-H_{Thie}), 7.13 (2H, t, J = 7.8 Hz, 3(5)-H_{Ph}), 7.07 (1H, dd, J = 5.0, 1.0 Hz, 4-H_{Thie}), 6.76 (1H, t, J = 7.4 Hz, 4-H_{Ph}), 6.62 (2H, d, J = 8.0 Hz, 2(6)-H_{Ph}), 5.32 (1H, s, HC-CN), 3.90 (1H, br.s, H-N), ^{13}C nmr (75 MHz): δ 144.4, 134.5, 129.6 (2C, +), 127.8 (+), 126.1 (+), 124.3 (+), 120.4 (+), 118.2, 114.3 (2C, +), 46.0 (+). ms: m/z: 214 (molecular ion). *Anal*. Calcd. for $C_{12}H_{10}N_2S$: C, 67.26; H, 4.70; N, 13.07. Found: C, 67.45; H, 4.76; N, 12.98.

2-(4-Chlorophenylamino)-2-(3-thienyl)acetonitrile (6c). The compound **6b** was obtained in 88 % yield, yellow oil. ^{1}H nmr (deuterium chloroform): δ 7.42 (1H, dd, J = 2.8, 1.6 Hz, 2-H_{Thie}), 7.28 (1H, dd, J = 5.0, 3.0 Hz, 5-H_{Thie}), 7.11-7.05 (3H, m, 4-H_{Thie}, and 3(5)-H_{Ar}), 6.56 (2H, d, J = 8.8 Hz, 2(6)-H_{Ar}), 5.28 (1H, d, J = 8.8 Hz, HC-CN), 3.98 (1H, d, J = 8.8 Hz, H-N), ^{13}C nmr (75 MHz): δ 143.0, 134.1, 129.5 (2C, +), 129.1, 127.9 (+), 126.0 (+), 125.3, 124.4 (+), 117.9, 115.5 (2C, +), 46.1 (+). ms: m/z: 248 (molecular ion). *Anal*. Calcd. for $C_{12}H_{10}ClN_2S$: C, 57.95; H, 3.65; N, 11.26. Found: C, 57.87; H, 3.94; N, 11.32.

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