Synthesis of Homo- and Heterobiarylmethylamines

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Abstract: A variety of homo- and heterobiarylmethylamines were prepared in modest to high yields via a convenient one-pot process.

Key words: biarylmethylamines, imines, nitriles, nucleophilic addition

Diarylmethylamines represent an important subclass of benzylic amines that can be divided into homobiarylmethylamines and heterobiarylmethylamines. The former are found in biologically active compounds such as the histamine H1-receptor antagonist cetirizine dihydrochloride[1] or the selective opioid receptor agonist SNC80.[2] The structures of heterobiarylmethylamines are characterized by the presence of one or two heterocycles. The propensity of homobiarylmethylamine subunits based on heterocycles to form transition metal complexes attracted much interest in recent years. For instance, palladium complexes efficiently catalyze the formation of C–C and C–N bonds.[3] Copper,[4] zinc[4] and ruthenium[5] complexes have been prepared and characterized. Moreover, vanadium[6] and iron[7] complexes of polydendate heterocyclic ligands based on homobiarylmethylamine moieties have been found to act as catalysts in oxidation reactions of various substrates, to mimic natural peroxidases and to cleave DNA. While variously substituted diphenylmethylamines **1** have been prepared, the heterobiarylmethylamine families are to date restricted to four azine-based skeletons **2**–**5** as shown below (Figure 1).

Surprisingly, homo- or heterodiarylmethylamines based on N, S, O five-membered heterocycles and polyheteroatomic heterocycles combinations remain unreported. Conceptually, approaches of their synthesis are based on nucleophilic additions to imine derivatives. Indeed, diphenylmethylamines were prepared by reacting benzonitrile and phenylmagnesium chloride followed by the reduction of the intermediate imine[8] or through catalytic addition of boronic acids to sulfinimes.[1] In the azine series, two- or three-step strategies, involving the isolation of ketone intermediates, the formation of the corresponding oximes followed by reduction, were mostly developed.[9]

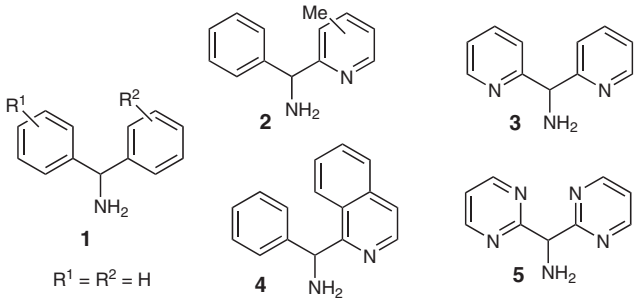
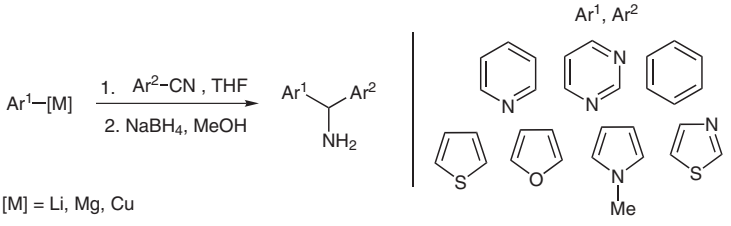


Figure 1 Biarylmethylamines **1**–**5**

We wish to report a general one-pot procedure providing homo- and heterobiarylmethylamines including mixed combinations of various heterocycles. The strategy is based on the direct addition of metalated (hetero)aromatics to aryl nitriles and the subsequent reduction of in situ generated imines by sodium borohydride (Scheme 1).

We first investigated the preparation of symmetric targets (Scheme 1: $Ar^1 = Ar^2$, Table 1). In the case of diphenylmethylamine **1**, several nucleophiles (Li, Mg, Cu) have been tested.[10] The best combination, involving phenylmagnesium chloride and benzonitrile in THF, afforded the expected compound in 64 to 73% yields. The amines were easily purified by careful acidic-basic treatment of the crude material. Arylmagnesium chlorides have been prepared using the aryl halide and either magnesium turnings



Scheme 1 General one-pot synthesis of biarylmethylamines

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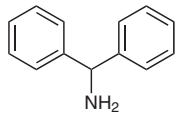
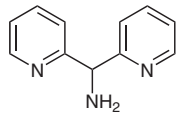
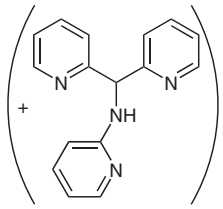
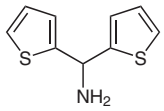
Table 1 Homobiarylmethylamines **1**, **3**, and **7** Prepared

Entry	$Ar^1 = Ar^2$	Homobiarylmethylamines		Yield (%)
1	Ph		**1**	64–73
2	2-pyridyl		**3**	53
			(**6**)	(28)[11]
3	2-thienyl		**7**	30

or isopropylmagnesium chloride. Activation of the nitrile moiety by addition of Lewis acids ($BF_3{\cdot}OEt_2$) did not improve yields.

Among the heterocyclic substrates studied, both pyridyl- and thienyllithium derivatives gave unsatisfactory results. Their addition to 2-cyanopyridine or 2-cyanothiophene, respectively, afforded low yields of the expected substituted methylamine and required tedious purification due to the presence of numerous side products such as **6** which was isolated in 28% yield.[11] Although the use of organomagnesium derivatives was preferred it did not completely avoid the formation of by-products such as 2,2′-bipyridine or 2,2′-bithiophene. Pyridyl- and thienylmagnesium chlorides were reacted with 2-cyanopyridine and 2-cyanothiophene, respectively, to afford the symmetric dipyridyl- and dithienylmethylamines **3** and **7** in 53 and 30% yield, respectively. The use of two or three fold excesses of the nucleophile with respect to the nitrile derivatives shows only moderate influence on the isolated yield of the corresponding methylamine. Moreover, increase of reaction times as well as inversion of mode of addition of both reactants did not improve the yield of compounds **3** and **7**.

We next turned our attention to unsymmetrical structures. In this series, targets have been envisioned through either cross (CA) and reverse cross-additions (RCA). New mixed diarylmethylamines have been obtained; their structures and yields of CA and RCA are gathered in Table 2. All diarylmethylamines could be obtained from both pathways. Yields ranged from 24 to 96% in case of cross addition and from 32 to 80% in case of reverse cross-additions. Only methylamine **15** could not be isolated (entry 8). Both cross addition and the reverse process cleanly afforded the expected product **15** as the major component of the crude material. Unfortunately, all attempts to purify the crude product only led to degradations. However, characteristic signals in ^1H and ^{13}C NMR spectra at 5.3 and 54.7 ppm, respectively, account for the benzylic CH moiety and evidenced the formation of the expected product.

The results gathered in Table 2 seem to indicate that CA is the preferred process in most cases, regardless of the π-acceptor or the π-donor character of the aromatic ring. If a marked effect is observed when π-acceptor heterocycles, such as pyridine or pyrimidine, are involved (Table 2, entries 1 and 2), the overall influence of electronic effects over the one-pot two-step process remains unclear. Indeed, in mixed π-acceptor and π-donor combinations (entries 6–9), electronic effects probably neutralize each other partially.

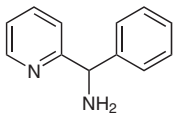
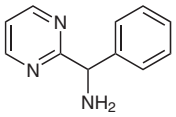
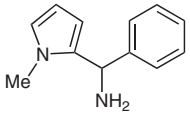
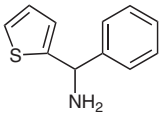
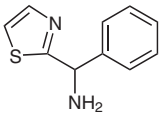
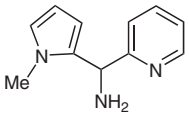
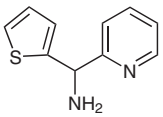
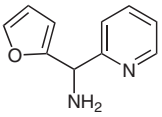
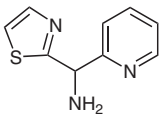
All new compounds were fully characterized. Both ^1H and ^{13}C NMR spectra show characteristic chemical shifts for diarylmethylamines **1**, **3** and **7**–**16** (Table 3). Benzylic H and C atoms resonate from 5.08 to 5.75 and from 52.0 to 61.9 ppm respectively. Interestingly the shielding of the benzylic carbon $\Delta\delta_C$ is in good agreement with the π-acceptor and π-donor character of the aromatic substituents (Table 3). Indeed, a clear difference appeared between π-acceptor and π-donor aromatics, the former being characterized by a positive shielding, while the later typically show a large negative shielding. If one compares the shielding values for compounds **13**, **14** and **16**, where both electronic effects are mixed, to **10**, **11** and **12**, respectively, an increase is observed reflecting an averaged influence of both heterocyclic partners.

In a similar way, the shielding of the benzylic proton $\Delta\delta_H$, except for the *N*-methylpyrrolyl substituent, seems also to be in agreement with the π-acceptor and π-donor character of the aromatic groups. For instance, in the presence of a pyridine or pyrimidine moiety a small difference of 0.02 and 0.09 ppm is noted. In comparison, π-donor substituents values of 0.24 and 0.27 were obtained for **11** and **12**. By replacing both phenyl groups in **1** for two thienyl groups affording **7**, the shielding observed increased to 0.52 ppm.

In conclusion, new homo-and heterobiarylmethylamines bearing combinations of π-acceptor/π-acceptor, π-donor/π-donor as well as mixed π-donor/π-acceptor aromatics have been successfully prepared. Targets could be obtained via the one pot nucleophilic addition-reduction sequence starting from aromatic and heterocyclic nitriles.

NMR spectra were recorded on a Bruker AC spectrometer at 200 MHz or 300 MHz (^1H) and 75 MHz (^{13}C). Mass spectra were recorded on a HP MS Eingin 5989B using a Brandford Analytica source. Solvents were freshly distilled prior to use. THF was distilled from sodium/benzophenone ketyl and MeOH was distilled from MgI_2. All other reagents were commercially available and were used as received. All reactions were carried out under argon, unless otherwise stated.

Table 2 Synthesis of Heterobiarylmethylamines Through Cross- and Reverse Cross-Additions

Entry	Ar^1	Ar^2	Diarylmethylamine		Yield (%)	
					CA	RCA
1	2-pyridyl	Ph		**8**	90	45
2	2-pyrimidyl	Ph		**9**	55	–[a]
3	2-pyrrolyl	Ph		**10**	24	32
4	2-thienyl	Ph		**11**	94	52
5	2-thiazolyl	Ph		**12**	91	80
6	2-pyrrolyl	2-pyridyl		**13**	56	–[b]
7	2-thienyl	2-pyridyl		**14**	96	56
8	2-furyl	2-pyridyl		**15**	–[c]	–[c]
9	2-thiazolyl	2-pyridyl		**16**	–[b]	64

[a] Product decomposed.
[b] Not determined.
[c] Not isolated.

Table 3 Benzylic Chemical Shifts for Products **1**–**16**

Entry	Nuclear	Chemical Shifts ($CDCl_3$, δ)										
		1	**3**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**16**
1	^1H	5.23	5.36	5.75	5.25	5.32	5.08	5.47	5.50	5.32	5.47	5.50
2	^{13}C	59.9	65.7	52.0	61.1	61.9	53.4	56.2	55.7	54.3	57.2	58.9
3	$\Delta\delta_C$	–	+5.8	–7.9	+1.2	+2.0	–6.5	–3.7	–4.2	–5.6	–2.7	–1.0
4	$\Delta\delta_H$	–	+0.13	+0.52	+0.02	+0.09	–0.15	+0.24	+0.27	+0.11	+0.24	+0.27

One-Pot Synthesis of Biarylmethylamines 1, 3, 7–14, 16; General Procedure

To a stirred solution of the aryl halide (5 mmol, 1 equiv) in anhyd THF (10 mL) was added isopropylmagnesium chloride (2 M in THF, 2.5 mL, 1 equiv). The mixture was stirred at r.t. for 2 h under argon. The aromatic nitrile (5 mmol, 1 equiv) was then added and the mixture stirred for 3 h. The solvent was removed by evaporation, and the residue dissolved in anhyd MeOH (20 mL). $NaBH_4$ (5 mmol, 1 equiv) was added and the mixture was stirred at r.t. for 16 h. After concentration under vacuum, 1 M HCl (20 mL) was added and the aqueous layer was washed with EtOAc (3 × 20 mL). The aqueous phase was basified with aq 3 M NaOH up to pH 9–10, and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under vacuum. The crude product was purified by flash chromatography (Tables 1 and 2).

Diphenylmethylamine (1)

Yield: 73%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.17 (br, 2 H, NH_2), 5.23 (s, 1 H, *H*CNH_2), 7.29–7.41 (m, 10 H_{arom}). Data are in accordance with previously reported results.[8b]

Di(2-pyridyl)methylamine (3)

Yield: 53%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.45 (br, 2 H, NH_2), 5.36 (s, 1 H, *H*CNH_2), 7.17 (dd, ^3J = 4.9, 7.6 Hz, 2 H, *H*CHCN), 7.43 (d, ^3J = 7.2 Hz, 2 H, *H*CHCHCHCN), 7.64 (t, ^3J = 7.4 Hz, 2 H, *H*CCHCHN), 8.55 (d, ^3J = 5.1 Hz, 2 H, HCN). Data are in accordance with previously reported results.[9b]

Di(2-thienyl)methylamine (7)

Yield: 30%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.84 (br, 2 H, NH_2), 5.72 (s, 1 H, *H*CNH_2), 6.95 (dd, ^3J = 3.6, 5.0 Hz, 2 H, *H*CHCS), 7.00 (m, 2 H, *H*CHCHCS), 7.24 (dd, ^3J = 1.3, 5.1 Hz, 2 H, HCS).

^{13}C{^{1}H} NMR ($CDCl_3$): δ = 52.0 (CNH_2), 124.1 (H*C*HCHCS), 124.6 (HCS), 126.7 (H*C*HCS), 149.9 (S*C*CH).

MS (EI, 70 eV): *m*/*z* (%) = 195 (M^+, 80), 194 (40), 179 ($M^+ - NH_2$, 80), 112 (M^+ – Thio, 70), 111 (100), 110 (90), 85 (90), 83 ($Thio^+$, 60).

MS (CI, NH_3): *m*/*z* (%) = 372 (20), 287 (20), 195 (30), 194 (30), 179 ($M^+ - NH_2$, 100), 111 (10).

MS (TOF, ES+): *m*/*z* (%) = 179 ($M^+ - NH_2$, 100).

2-Pyridylphenylmethylamine (8)

Yield: 90%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.33 (br, 2 H, NH_2), 5.28 (s, 1 H, *H*CNH_2), 7.16 (t, ^3J = 6.1 Hz, 1 H, *H*CHCN), 7.28 (m, 2 H, $H_{arom\text{-}p}$ and *H*CHCHCHCN), 7.35 (t, ^3J = 7.6 Hz, 2 $H_{arom\text{-}m}$), 7.45 (d, ^3J = 7.7 Hz, 2 $H_{arom\text{-}o}$), 7.62 (t, ^3J = 7.7 Hz, 1 H, *H*CHCHCN), 8.60 (d, ^3J = 3.8 Hz, 1 H, HCN). Data are in accordance with previously reported results.[9c]

2-Pyrimidylphenylmethylamine (9)

Yield: 55%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.16 (br, 2 H, NH_2), 5.32 (s, 1 H, *H*CNH_2), 7.06 (t, ^3J = 4.9 Hz, 1 H, *H*CHCN), 7.22 (d, ^3J = 7.1 Hz, 1 $H_{arom\text{-}p}$), 7.30 (t, ^3J = 7.3 Hz, 2 $H_{arom\text{-}m}$), 7.43 (d, ^3J = 6.9 Hz, 2 $H_{arom\text{-}o}$), 8.64 (d, *J* = 5.0 Hz, 2 H, HCN).

^{13}C{^{1}H} NMR ($CDCl_3$): δ = 61.5 (CNH_2), 119.2 (H*C*HCN), 126.9 (2 $CH_{arom\text{-}o}$), 127.4 (C-8), 128.6 ($CH_{arom\text{-}p}$), 144.1 ($C_{arom\text{-}ipso}$), 157.2 (HCN), 171.7 (NCN).

MS (EI, 70 eV): *m*/*z* (%) = 185 (M^+, 30), 169 ($M^+ - NH_2$, 10), 108 (M^+ – Ph, 30), 106 (M^+ – Pyr, 100), 85 (40), 83 (50), 79 (Pyr^+, 50), 77 (Ph^+, 40), 51 (10).

MS (CI, NH_3): *m*/*z* (%) = 186 (M + H^+, 100), 185 (70), 184 (30), 169 ($M^+ - NH_2$, 50), 106 (M^+ – Pyr, 60).

MS (TOF, ES+): *m*/*z* (%) = 407 (10), 352 (10), 186 (M + H^+, 10), 169 ($M^+ - NH_2$, 100).

2-(*N*-Methylpyrrolyl)phenylmethylamine (10)

Yield: 32%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.79 (br, 2 H, NH_2), 3.35 (s, 3 H, CH_3), 5.08 (s, 1 H, *H*CNH_2), 5.96–6.02 (m, 2 H, *H*CHCN and *H*CHCHCN), 6.48 (t, ^3J = 2.2 Hz, 1 H, HCN), 7.16–7.22 (m, 5 H, C_6H_5).

^{13}C{^{1}H} NMR ($CDCl_3$): δ = 34.1 (NCH_3), 53.4 (CNH_2), 106.5 (H*C*HCHCN), 106.6 (H*C*HCN), 122.6 (HCN), 127.1 (2 $CH_{arom\text{-}m}$), 127.2 ($CH_{arom\text{-}p}$), 128.6 (2 $CH_{arom\text{-}o}$), 136.0 (N*C*CH), 144.3 ($C_{arom\text{-}ipso}$).

MS (EI, 70 eV): *m*/*z* (%) = 186 (M^+, 50), 170 ($M^+ - NH_2$, 50), 156 (40), 109 (M^+ – Ph, 100), 82 (60).

2-Thienylphenylmethylamine (11)

Yield: 94%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.08 (br, 2 H, NH_2), 5.44 (s, 1 H, *H*CNH_2), 6.88 (d, ^3J = 3.2 Hz, 1 H, *H*CHCHCS), 6.97 (t, ^3J = 3.5 Hz, 1 H, *H*CHCS), 7.24 (d, ^3J = 3.8 Hz, 1 H, HCS), 7.33 (d, ^3J = 6.8 Hz, 1 $H_{arom\text{-}p}$), 7.40 (t, *J* = 7.4 Hz, 2 $H_{arom\text{-}m}$), 7.47 (d, *J* = 7.5 Hz, 2 $H_{arom\text{-}o}$).

^{13}C{^{1}H} NMR ($CDCl_3$): δ = 56.2 (CNH_2), 123.9 (H*C*HCHCS), 124.4 (HCS), 126.6 (H*C*HCS), 126.7 (2 $CH_{arom\text{-}o}$), 127.5 ($CH_{arom\text{-}p}$), 128.6 (2 $CH_{arom\text{-}m}$), 145.3 ($C_{arom\text{-}ipso}$), 150.1 (S*C*CH).

MS (EI, 70 eV): *m*/*z* (%) = 189 (M^+, 100), 173 ($M^+ - NH_2$, 20), 112 (M^+ – Ph, 60), 104 (50), 85 (30), 77 (Ph^+, 30), 51 (20).

MS (TOF, ES+): *m*/*z* (%) = 299 (20), 173 ($M^+ - NH_2$, 100).

2,2′-Thiazolylbenzylamine (12)

Yield: 80%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.23 (br, 2 H, NH_2) 5.50 (s, 1 H, HCNH_2), 7.24 (d, ^3J = 3.1 Hz, 1 H, HCS), 7.29–7.39 (m, 3 H, C_6H_5), 7.46–7.49 (m, 2 H, C_6H_5), 7.72 (d, ^3J = 3.1 Hz, 1 H, HCN).

^{13}C{^{1}H} NMR ($CDCl_3$): δ = 55.7 (CNH_2), 116.5 (CHS), 124.4 (2 $CH_{arom\text{-}o}$), 125.4 ($CH_{arom\text{-}p}$), 126.3 (2 $CH_{arom\text{-}m}$), 140.2 (HCN), 140.6 ($C_{arom\text{-}ipso}$), 173.8 (SCN).

MS (EI, 70 eV): *m*/*z* (%) = 361 (2 $M^+ - NH_3 - H$, 25), 276 (100), 190 (M^+, 10), 174 ($M^+ - NH_2$, 95), 77 (Ph^+, 20).

MS (CI, NH_3): *m*/*z* (%) = 362 (100), 361 (60), 277 (30), 276 (60), 174 (M – NH_2, 40).

MS (TOF, ES+): *m*/*z* (%) = 362.1 (100) 174.0 (95).

2-(*N*-Methylpyrrolyl)-2′-pyridylmethylamine (13)

Yield: 56%.

^{1}H NMR (300 MHz, $CDCl_3$): δ= 2.94 (br, 2 H, NH_2), 3.54 (s, 3 H, CH_3), 5.32 (s, 1 H, *H*CNH_2), 5.98 (dd, ^3J = 2.0, 3.5 Hz, 1 H, *H*CHCNMe), 6.07 (t, ^3J = 3.2 Hz, 1 H, *H*CHCHCNMe), 6.58 (t, ^3J = 2.2 Hz, 1 H, *H*CNMe), 7.14–7.21 (m, 2 H, *H*CHCHCHCN and *H*CHCN), 7.63 (t, ^3J = 7.5 Hz, 1 H, *H*CHCHCN), 8.58 (d, ^3J = 4.6 Hz, 1 H, HCN).

^{13}C{^{1}H} NMR ($CDCl_3$): δ = 34.3 (NCH_3), 54.3 (CNH_2), 106.8 (H*C*HCHCNMe), 107.1 (H*C*HCNMe), 121.7 (H*C*HCN), 122.2 (H*C*HCHCHCN), 122.9 (H*C*NMe), 134.5 (MeN*C*CH), 136.8 (H*C*HCHCN), 148.9 (H*C*N), 162.3 (N*C*CH).

MS (EI, 70 eV): *m*/*z* (%) = 187 (M^+, 30), 170 (20), 109 (M^+ – Pyr, 100), 108 (40), 82 (50).

2-Thienyl-2′-pyridylmethylamine (14)
Yield: 69%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.28 (br, 2 H, NH_2), 5.47 (s, 1 H, *H*CNH$_2$), 6.89–6.95 (m, 2 H, *H*CHCHCS and *H*CHCS), 7.14–7.22 (m, 2 H, *H*CS and *H*CHCN), 7.32 (d, ^3J = 7.9 Hz, 1 H, *H*CHCHCHCN), 7.64 (t, ^3J = 7.7 Hz, 1 H, *H*CHCHCN), 8.57 (d, ^3J = 4.8 Hz, 1 H, HCN).

^{13}C{^{1}H} NMR ($CDCl_3$): δ = 57.2 (CNH_2), 121.4 (H*C*HCHCHCN), 122.4 (H*C*HCN), 124.2 (H*C*HCHCS), 124.8 (HCS), 126.7 (H*C*HCS), 136.8 (H*C*HCHCN), 149.2 (S*C*CH), 149.3 (H*C*N), 162.8 (N*C*CH).

MS (EI, 70 eV): *m*/*z* (%) = 190 (M^+, 40), 174 ($M^+ - NH_2$, 20), 112 (M^+ – Pyr, 100), 105 (20), 85 (60), 79 (30), 78 (Pyr^+, 40), 51 (20).

MS (TOF, ES+): *m*/*z* (%) = 174 ($M^+ - NH_2$, 100).

2-Thiazolyl-2′-pyridylmethylamine (16)
Yield: 56%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.70 (br, 2 H, NH_2), 5.49 (s, 1 H, *H*CNH$_2$), 7.20 (dd, ^3J = 4.8, 7.5 Hz, 1 H, *H*CHCN), 7.26 (d, ^3J = 3.3 Hz, 1 H, *H*CS), 7.42 (d, ^3J = 7.9 Hz, 1 H, *H*CHCHCHCN), 7.65 (t, ^3J = 7.7 Hz, 1 H, *H*CHCHCN), 7.71 (d, ^3J = 3.5 Hz, 1 H, *H*CHCS), 8.58 (d, ^3J = 4.8 Hz, 1 H, HCN).

^{13}C{^{1}H} NMR ($CDCl_3$): δ = 58.9 (CNH_2), 119.3 (HCS), 122.0 (H*C*HCN), 122.7 (H*C*HCHCHCN), 136.8 (H*C*HCHCN), 142.6 (H*C*HCS), 149.4 (HCN), 160.5 (N*C*CH), 175.5 (NCS).

MS (EI, 70 eV): *m*/*z* (%) = 191 (M^+, 10), 190 (30), 175 ($M^+ - NH_2$, 10), 162 (40), 161 (20), 112 (20), 105 (20), 79 (30), 78 (Pyr^+, 100), 58 (30), 51 (30).

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