Strecker-Type Reaction of Nitrones Using Cyanohydrin

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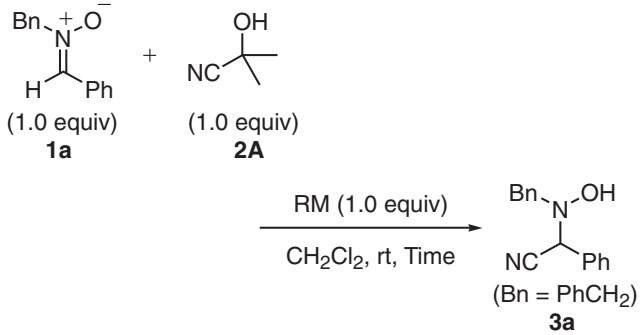
Strecker-type reaction of nitrones using acetone cyanohydrin as a cyanide source was developed. By treating nitrones with acetone cyanohydrin in the presence of *n*-BuMgCl, transcyanation from the cyanohydrin to the nitrones smoothly proceeded in THF at 35 °C. The amount of *n*-BuMgCl could be reduced to 0.2 equiv to give the corresponding α-cyanohydroxylamines in up to 98% yields.

The Strecker-type hydrocyanation of carbon–nitrogen double bonds is one of the oldest methods for the preparation of α-amino nitriles,[1] which are versatile synthetic intermediates for α-amino acids and various nitrogen-containing heterocycles such as imidazoles and thiadiazoles.[1,2] Among organic nitrogen compounds bearing a carbon–nitrogen double bond, a nitrone seems to be a suitable substrate as it possesses electronegative oxygen, which is coordinatable to metals and polarizes a carbon–nitrogen double bond to effectively enhance the electrophilic reactivity. Nucleophilic addition to nitrones affords various types of hydroxylamines, which are useful compounds for the preparation of nitrogen-containing chemicals.[3] We have developed various types of nucleophilic addition reactions to nitrones.[4] The Strecker-type reaction of nitrones is also a useful way to prepare α-amino nitrile derivatives, however, only a few reports have appeared for the addition to nitrone using hydrogen cyanide that was generated in situ from potassium cyanide[5] or trimethylsilyl cyanide[6] as a cyanide source. Hydrogen cyanide and trimethylsilyl cyanide are the most commonly used cyanide sources for the Strecker-type reaction, however, some problems such as high toxicity, volatility, expense, and difficulty to handle, are still associated with these approaches. In this regard, the development of other cyanide sources for Strecker-type reaction has been explored including the use of tributyltin cyanide,[7] diethylaluminum cyanide,[8] diethyl phosphorocyanidate,[9] ethyl cyanoformate,[10] and acyl cyanide.[11] Among such cyanide compounds, acetone cyanohydrin is one of the simplest, stable, relatively less toxic, easy to handle, and readily available cyanide sources.[12] Herein we disclose the Strecker-type reaction of nitrones by the use of acetone cyanohydrin as a cyanide source.

Results and Discussion

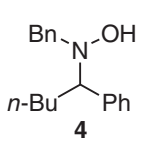
First acetone cyanohydrin (**2A**) was treated with (*Z*)-benzyl(benzylidene)amine *N*-oxide (**1a**) in CH_2Cl_2 at rt. The reaction did not occur at all and the nitrone **1a** was recovered after 17 h (Table 1, Entry 1). Then the Strecker-type reaction was carried out via generation of the corresponding metal alkoxide of acetone cyanohydrin (**2A**) by the treatment with appropriate metallic reagents (Entries 2–11).[13] When **2A** was treated with NaH, the Strecker-type reaction did not proceed either (Entry 2). A desired cyano-transferred product **3a** was observed when **2A** was treated with MeMgBr (Entry 3). By the use of *n*-BuMgCl as a metal source, the reaction proceeded

Table 1. The Strecker-Type Reaction of Nitrone **1a** Using Acetone Cyanohydrin (**2A**) as a Cyanide Source



Entry	RM	Time/h	Yield/%
1	—	17	no reaction
2	NaH	45	no reaction
3	MeMgBr	20	16
4	*n*-BuMgCl	43	54
5	*n*-Bu_2Mg	18	17[a)]
6	Me_3Al	65	48
7	Et_2AlCl	43	29
8	Me_2Zn	44	no reaction
9	MeZnBr[b)]	41	no reaction
10	(*i*-PrO)$_4$Ti	43	no reaction
11	(*i*-PrO)$_3$Sm	20	—[c)]

a) By-product **4** was obtained in 18% yield. b) MeZnBr was prepared in situ from 0.5 equiv of Me_2Zn and 0.5 equiv of $ZnBr_2$. c) An imine **5** was obtained in less than 17% yield.



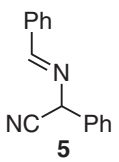


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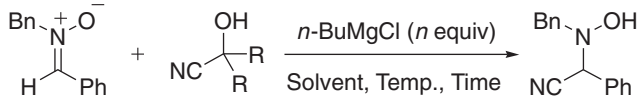
Table 2. The Transcyanation of Cyanohydrin **2** by the Treatment with *n*-BuMgCl



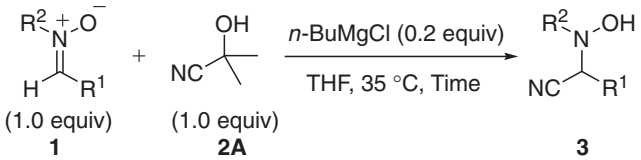
Entry	R	R	2	*n*	Solvent	Temp/°C	Time/h	Yield/%
1	CH_3	CH_3	**A**	1.0	toluene	rt	43	67
2	CH_3	CH_3	**A**	1.0	CH_2Cl_2	rt	43	54
3	CH_3	CH_3	**A**	1.0	MeCN	rt	43	41
4	CH_3	CH_3	**A**	1.0	Et_2O	rt	43	59
5	CH_3	CH_3	**A**	1.0	THF	rt	49	75
6	CH_3	CH_3	**A**	1.0	THF	35	26	81
7	CH_3	CH_3	**A**	1.0	THF	60	29	81
8	CH_3	CH_3	**A**	0.2	THF	35	23	90
9	CH_3	CH_3	**A**	0.1	THF	35	115	23
10	$-(CH_2)_5-$		**B**	1.0	THF	35	20	60
11	$-(CH_2)_5-$		**B**	0.2	THF	35	44	no reaction

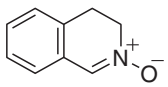
more smoothly to give **3a** in 54% yield (Entry 4). The reaction using *n*-Bu_2Mg gave a butylated by-product **4**[14] in addition to the desired product **3a** (Entry 5). Generation of aluminum alkoxide by the treatment with Me_3Al or Et_2AlCl was also effective to give **3a** in 48% or 29% yield, respectively (Entries 6 and 7). Zinc reagents, Me_2Zn and MeZnBr, and titanium alkoxide, $(i\text{-PrO})_4Ti$ were not effective at all (Entries 8–10). In the case of $(i\text{-PrO})_3Sm$, the expected cyanation itself proceeded, but was followed by the dehydration to give an imine **5**[15] in less than 17% yield (Entry 11).

Next the Strecker-type reaction of nitrone **1a** was carried out with acetone cyanohydrin (**2A**) and 1.0 equiv of *n*-BuMgCl in other solvents. Among the solvents examined, THF realized the highest chemical yield as shown in Table 2. When *n*-BuMgCl was treated with cyanohydrin **2A** in THF, the solution became cloudy probably due to the formation of chloromagnesium salt of **2A**. However, after the addition of the nitrone **1a**, the reaction mixture gradually became clear. In order to promote the reaction, temperature was raised up to 35 °C. The product **3a** was obtained in 81% yield (Entry 6). Enhancement of the temperature to 60 °C did not improve the chemical yield any more (Entry 7). Furthermore, the amount of *n*-BuMgCl could be decreased to 0.2 equiv producing **3a** in 90% yield (Entry 8), however, the use of less *n*-BuMgCl lowered the chemical yield remarkably (Entry 9). As a cyanide source, cyclohexanone cyanohydrin (**2B**) was not so effective (Entries 10 and 11): Even when 1.0 equiv of *n*-BuMgCl was used, the yield of **3a** was only 60%.

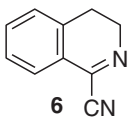
The magnesium-mediated Strecker-type cyanation of various nitrones **1** was performed with 1.0 equiv of acetone cyanohydrin (**2A**) and 0.2 equiv of *n*-BuMgCl in THF at 35 °C, and the results are summarized in Table 3. The reaction of *p*-methoxy- and *p*-chloro-substituted nitrones on aromatic ring **1b** and **1c** gave the products **3b** and **3c** in good yields (Entries 2 and 3). In the case of nitrone **1d** derived from acetaldehyde, the Strecker-type reaction proceeded well to afford the product **3d** in 98% yield (Entry 4). The cyanation of cyclohexyl- and

Table 3. The Strecker-Type Reaction of Nitrones **1**



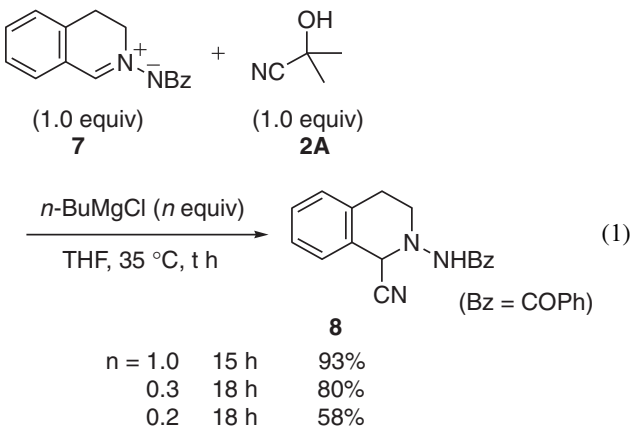
Entry	R^1	R^2	1	Time/h	Yield/%
1	Ph	Bn	**a**	23	90
2	*p*-$MeOC_6H_4$	Bn	**b**	14	73
3	*p*-ClC_6H_4	Bn	**c**	14	81
4	Me	Bn	**d**	16	98
5	*c*-Hex	Bn	**e**	18	84
6	*t*-Bu	Bn	**f**	16	93
7	Ph	Me	**g**	16	86
8	Ph	Ph	**h**	18	85
9			**i**	18	—[a]

a) A dehydrated product **6** was obtained in less than 13% yield.



t-butyl-substituted nitrones **1e** and **1f** also proceeded smoothly (Entries 5 and 6). The substituents on the nitrogen atom of nitrone **1** did not affect the reaction (Entries 7 and 8). Cyanation of a cyclic nitrone, 3,4-dihydroisoquinoline *N*-oxide (**1i**), was sluggish and gave a dehydrated imine **6**[5c] in poor yield (Entry 9).

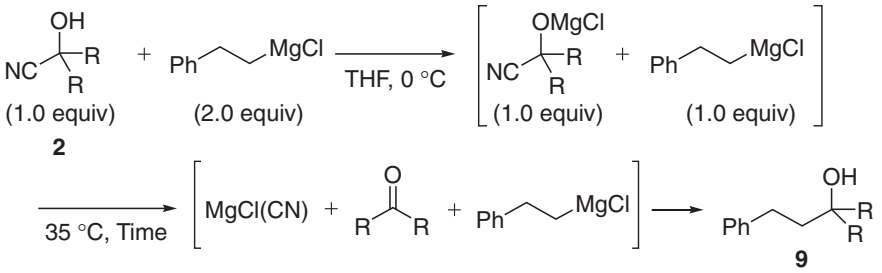
In order to prepare the 1-cyano-substituted isoquinoline skeleton, other acceptors were surveyed. It was found that an azomethine imine **7**[16] instead of the nitrone **1i** afforded the corresponding α-cyanated product **8** without elimination in good yield (eq 1).



(1)

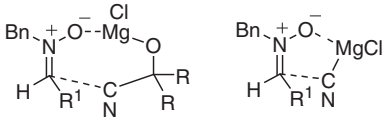
For the present Strecker-type reaction, two types of mechanism might be possible; one is a cyclic transfer mechanism **A** and another is a mechanism **B** via magnesium cyanide generated from chloromagnesium salt of cyanohydrin accompanied by release of the corresponding ketone. In order to confirm the mechanism, the Strecker-type reaction was carried out using optically active (*R*)-mandelonitrile (**2C**). When **2C**

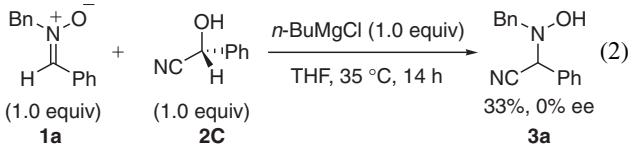
Table 4. Reactions of Cyanohydrins **2** with 2 equiv of Grignard Reagent



Entry	R	R		Time/h	Yield of **9**/%
1	CH_3	CH_3	**A**	16	55
2	CH_3	CH_3	**A**	26	52
3	$-(CH_2)_5-$		**B**	16	94

was treated with 0.2 equiv of *n*-BuMgCl, transcyanation to **1a** did not proceed.[17] Therefore 1.0 equiv of *n*-BuMgCl was used toward (*R*)-**2C**, but the resulting adduct **3a** obtained in 33% yield was racemic and chiral induction was not observed (eq 2). This result seemed to support the mechanism **B**.





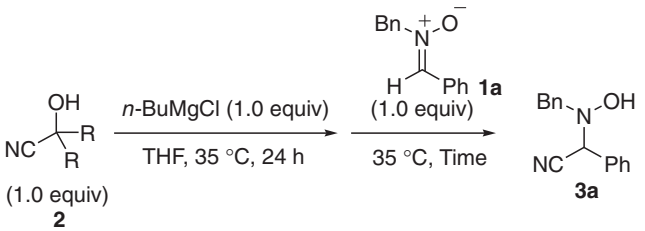
(2)

In order to get further information, several reactions were carried out. First, cyanohydrins **2** were treated with 2 equiv of chloro(2-phenylethyl)magnesium. If chloromagnesium cyanide is generated with the release of ketones, the ketones could be trapped by excess Grignard reagent to give tertiary alcohols **9**. In the case of acetone cyanohydrin (**2A**), the alcohol **9A**[18a] was obtained in 55% yield after 16 h. However, the production of **9A** was not increased after 26 h (Table 4, Entries 1 and 2). In the case of cyclohexanone cyanohydrin (**2B**), **9B**[18b] was obtained in over 90% yield after 16 h (Entry 3). These results suggested that chloromagnesium cyanide was produced in ca. 50% yield from **2A** and almost quantitatively from **2B**, respectively.

Next, the Strecker-type reaction was performed by pretreatment of cyanohydrins **2** with Grignard reagent at 35 °C for 24 h to produce chloromagnesium cyanide before the addition of the nitrone. In the case of acetone cyanohydrin (**2A**), the reaction appeared to proceed similarly and it took almost the same reaction time to complete the reaction (Table 5, Entry 1 and Table 2, Entry 6). By the use of cyclohexanone cyanohydrin (**2B**), from which chloromagnesium cyanide might be generated in situ almost quantitatively, chemical yield was enhanced, but still lower than that using **2A** (Table 5, Entry 2 and Table 2, Entry 10).

Although the precise mechanism is still not fully understood, the present reaction would proceed via both transition states **A** and **B** based on the results described above.

Table 5. The Transcyanation by Pretreatment of Cyanohydrin **2** with *n*-BuMgCl



Entry	R	R	**2**	Time/h	Yield/%
1	CH_3	CH_3	**A**	26	84
2	$-(CH_2)_5-$		**B**	20	73

In the reaction using 0.2 equiv of Grignard reagent, regeneration of the chloromagnesium salt of cyanohydrin by the reaction of the produced chloromagnesium salt of **3** with unreacted cyanohydrin makes the catalytic cycle possible.

As described above, the efficient Strecker-type reaction of nitrones using acetone cyanohydrin could be developed. Transformation of acetone cyanohydrin into its chloromagnesium salt by treating with *n*-BuMgCl was effective to afford the cyanated products in high yields. In the case of 3,4-dihydroisoquinoline derivative, the corresponding azomethine imine instead of the nitrone was the suitable substrate for the present cyanation to afford the α-cyanotetrahydroisoquinoline compound in good chemical yield.

Experimental

The ^{1}H NMR spectra were recorded on a JEOL ECS 400 NMR (400 MHz) spectrometer. The chemical shifts were determined in the δ-scale relative to TMS ($\delta = 0$) as an internal standard. The IR spectra were measured on a JASCO FT/IR-230 spectrometer. THF and Et_2O were freshly distilled over sodium diphenyl ketyl. All other solvents were distilled and stored over drying agents. Merck silica gel 60 PF_{254} (Art. 7749) and Cica silica gel 60N, spherical neutral (37563-84) were used for thin-layer chromatography (TLC) and flash column chromatography, respectively. All of the melting points were determined with a micro melting apparatus (Yanagimoto-Seisakusho) and are uncorrected.

A Representative Procedure for the Strecker-Type Reaction of 1a. To a solution of acetone cyanohydrin (**2A**) (43 mg, 0.5 mmol) in THF (3 mL), a solution of *n*-BuMgCl in THF (0.91 M, 0.11 mL, 0.1 mmol) was added at 0 °C under an argon atmosphere, and the mixture was allowed to stir for 1 h. The reaction mixture was warmed to 35 °C, and a solution of (*Z*)-benzyl(benzylidene)amine *N*-oxide (**1a**) (106 mg, 0.5 mmol) in THF (3 mL) was added. After 23 h, the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with AcOEt. The combined organic extracts were washed with brine, and then dried over Na_2SO_4. The solvent was evaporated and the residue was separated by TLC on SiO_2 (Hexane/AcOEt = 3/1, v/v) to afford **3a** (107 mg, 0.45 mmol) in 90% yield as a white solid.

In a similar manner, α-cyanohydroxylamines **3b**–**3h** and 1-cyanotetrahydroisoquinoline derivative **8** were prepared from the corresponding nitrones **1b**–**1h** and azomethine imine **7**, respectively.

2-[Benzyl(hydroxy)amino]-2-phenylacetonitrile (3a): Mp 116–117 °C (from *i*-PrOH). IR (KBr): 3400, 2919, 2864, 2245, 1604, 1496, 1453, 1070, 1031, 1011, 757, 740, 693 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.87 (s, 2H), 4.72 (s, 1H), 5.91 (br, 1H), 7.30–7.39 (m, 5H), 7.40–7.43 (m, 3H), 7.45–7.48 (m, 2H). Found: C, 75.42; H, 6.00; N, 11.46%. Calcd for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76%.

2-[Benzyl(hydroxy)amino]-2-(4-methoxyphenyl)acetonitrile (3b): Mp 98–100 °C (from *i*-PrOH). IR (KBr): 3426, 2234, 1612, 1513, 1456, 1244, 1021, 804, 751, 699 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.77 (s, 3H), 3.81 (s, 2H), 4.59 (s, 1H), 6.23 (br, 1H), 6.89 (d, 2H, J = 8.7 Hz), 7.27–7.35 (m, 7H). Found: C, 71.69; H, 6.06; N, 10.39%. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44%.

2-[Benzyl(hydroxy)amino]-2-(4-chlorophenyl)acetonitrile (3c): Mp 114–116 °C (from *i*-PrOH). IR (KBr): 3366, 3030, 2911, 2844, 2251, 1600, 1578, 1494, 1405, 1094, 795, 757, 727, 700 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.88 (d, 1H, J = 12.6 Hz), 3.96 (d, 1H, J = 12.6 Hz), 4.74 (s, 1H), 5.64 (br, 1H), 7.28–7.41 (m, 9H). Found: C, 66.04; H, 4.83; N, 10.20%. Calcd for $C_{15}H_{13}N_2OCl$: C, 66.06; H, 4.80; N, 10.27%.

2-[Benzyl(hydroxy)amino]propanenitrile (3d): Mp 97–99 °C (from *i*-PrOH). IR (KBr): 3237, 3033, 2944, 2899, 2238, 1496, 1457, 1446, 1376, 1113, 829, 739, 701 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.44 (d, 3H, J = 7.3 Hz), 3.65 (q, 1H, J = 7.3 Hz), 3.80 (d, 1H, J = 12.4 Hz), 3.99 (d, 1H, J = 12.4 Hz), 6.17 (br, 1H), 7.27–7.37 (m, 5H). Found: C, 68.28; H, 6.85; N, 15.91%. Calcd for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.90%.

2-[Benzyl(hydroxy)amino]-2-cyclohexylacetonitrile (3e): Mp 124–125 °C (from *i*-PrOH). IR (KBr): 3402, 2929, 2851, 2242, 1495, 1452, 1408, 738, 698 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.83–0.93 (m, 1H), 0.97–1.07 (m, 1H), 1.10–1.34 (m, 3H), 1.66–1.89 (m, 4H), 1.99–2.05 (m, 2H), 3.26 (d, 1H, J = 10.1 Hz), 3.82 (d, 1H, J = 12.8 Hz), 4.09 (d, 1H, J = 12.8 Hz), 5.42 (br, 1H), 7.28–7.34 (m, 5H). Found: C, 73.55; H, 8.29; N, 11.37%. Calcd for $C_{15}H_{20}N_2O$: C, 73.74; H, 8.25; N, 11.47%.

2-[Benzyl(hydroxy)amino]-3,3-dimethylbutanenitrile (3f): Mp 112–113 °C (from *i*-PrOH). IR (KBr): 3418, 2965, 2889, 2239, 1497, 1458, 1404, 1369, 1310, 740, 720 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.08 (s, 9H), 3.33 (s, 1H), 3.84 (d, 1H, J = 12.6 Hz), 4.14 (d, 1H, J = 12.6 Hz), 5.09 (br, 1H), 7.27–7.35 (m, 5H). Found: C, 71.31; H, 8.41; N, 12.67%. Calcd for $C_{13}H_{18}N_2O$: C, 71.53; H, 8.31; N, 12.83%.

2-[Hydroxy(methyl)amino]-2-phenylacetonitrile (3g): Mp 118–119 °C (from *i*-PrOH). IR (KBr): 3242, 2968, 2930, 2883, 2241, 1496, 1455, 1422, 1138, 1060, 967, 939, 748, 696 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.68 (s, 3H), 4.84 (s, 1H), 5.95 (br, 1H), 7.38–7.45 (m, 3H), 7.48–7.50 (m, 2H). Found: C, 66.61; H, 6.30; N, 17.16%. Calcd for $C_9H_{10}N_2O$: C, 66.65; H, 6.21; N, 17.27%.

2-[Hydroxy(phenyl)amino]-2-phenylacetonitrile (3h): Mp 120–121 °C (from *i*-PrOH). IR (KBr): 3271, 3054, 2245, 1594, 1489, 1454, 1187, 1170, 1010, 947, 768, 738 cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.38 (s, 1H), 5.56 (br, 1H), 7.15 (t, 1H, J = 7.3 Hz), 7.26 (d, 2H, J = 8.2 Hz), 7.35 (dd, 2H, J = 8.2, 7.3 Hz), 7.41–7.51 (m, 3H), 7.54–7.60 (m, 2H). Found: C, 75.13; H, 5.46; N, 12.48%. Calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49%.

***N*-[1-Cyano-3,4-dihydroisoquinolin-2(1*H*)-yl]benzamide (8):** Mp 146–147 °C (from AcOEt). IR (KBr): 3207, 3050, 2225, 1640, 1536, 1454, 1311, 921, 769, 745, 728, 692 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.63 (br, 1H), 2.94–3.00 (m, 1H), 3.28–3.37 (m, 2H), 3.51–3.57 (m, 1H), 5.50 (s, 1H), 7.19–7.33 (m, 4H), 7.47 (t, 2H, J = 7.3 Hz), 7.56 (t, 1H, J = 7.3 Hz), 7.82 (d, 2H, J = 7.3 Hz). Found: C, 73.74; H, 5.52; N, 15.14%. Calcd for $C_{17}H_{15}N_3O$: C, 73.63; H, 5.45; N, 15.15%.

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