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Carbon Dioxide: A Reagent for the Simultaneous Protection of Nucleophilic Centres and the Activation of Alternative Locations to Electrophilic Attack. Part III [1]. A New Synthetic Method for the ortho-Substitution of N-Monoalkylanilines

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Abstract

N-Methyl- and N-ethyl-aniline are regiospecifically converted into a range of ortho-substituted derivatives, using carbon dioxide both for N-protection and as an intermediate carbanion stabilizing group, and t-butyllithium to lithiate the ortho-carbon atom. The resulting lithium N-(ortho-substituted-phenyl)-N-methyl- and -N-ethyl-carbamates undergo smooth acid-catalysed decarboxylation under mild conditions. No alpha-substituted products were detected.

ortho-Substituted anilines are important key starting materials for the preparation of numerous heterocyclic compounds[2a] including important pharmaceuticals[2b].

Available methods for the regiospecific ortho-functionalization of primary and secondary aromatic amines has recently been expanded significantly by the introduction of the following techniques:

a) [2, 3]-sigmatropic rearrangement of azasulfonium ylides[3,4], e.g., N-phenyl-S,S-dimethylsulfilimide;

b) reaction of anilinodichloroborane with electrophiles[5];

c) heteroatom-facilitated dilithiation of aromatic amines followed by reaction with electrophiles[6], e.g. N-2-naphthylaniline;

d) heteroatom-facilitated lithiation of N-protected aromatic amines followed by reaction with electrophiles,[7], [8], [9], e.g. N-pivaloylaniline.

Method a) requires rather harsh reaction conditions for the desulfurization step after rearrangement and this limits its application. Method b) can in principle give the corresponding N-substituted aniline as a side product because anilinodichloroborane has two nucleophilic sites, i.e. the ortho-carbon and the nitrogen atom. In the published work, few electrophiles were examined. Method c) is apparantly limited to N-2-naphthylaniline and its analogs: the dilithiation of aniline and N-monoalkylanilines has not been reported to our knowledge. It is to be expected that rather drastic reaction conditions would be required for such dilithiations.

Method d) thus is the most attractive route so far reported to ortho-substituted anilines because there is only one nucleophilic site and

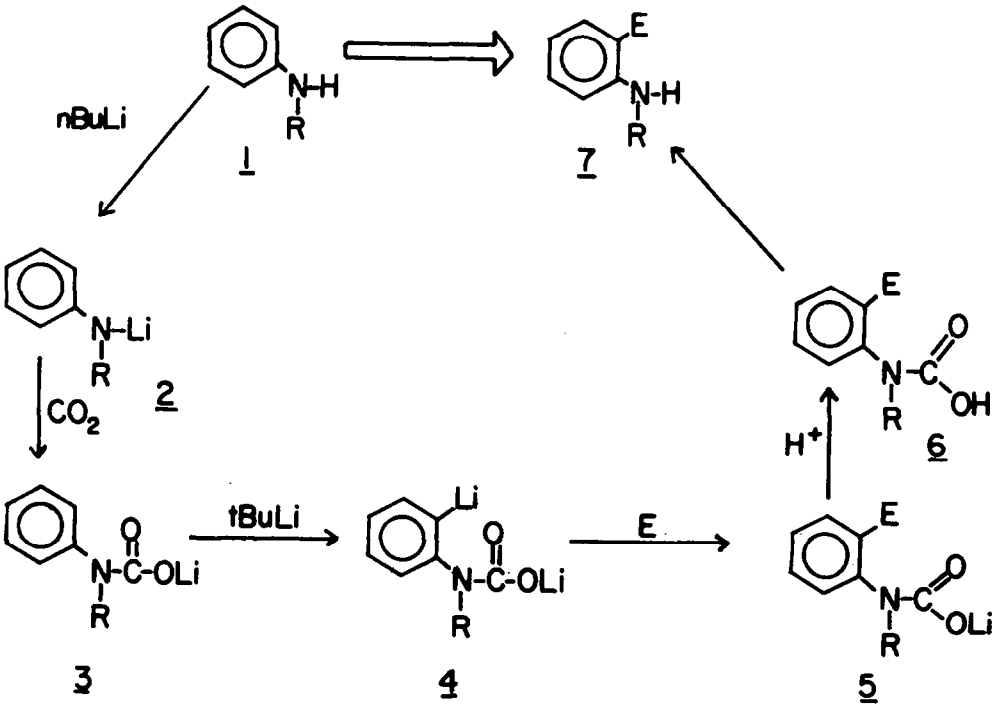
this is expected to provide selective ortho-functionalization of suitably N-protected N-monoalkylanilines. However, method d) requires three steps for protection, functionalization, and deprotection.

We have already reported that carbon dioxide provides excellent protection for the functionalization of the alpha-position of indole via the corresponding lithio species[10]. We have now studied the lithiation of lithium N-phenyl-N-alkylcarbamates derived from N-methyl- and of N-ethyl-aniline as an extension of the scope of our protection methodology. Recently, Seebach[11] and Meyers[12] independently reported the selective alpha-lithiation at the N-methyl group of N-nitroso-N-methylaniline and N-phenyl-N-methyl-N'-t-butylformamidine respectively. We anticipated that lithiation might occur at the N-methyl group of N-phenyl-N-methylcarbamates by analogy to their results. However, careful investigation of the lithiation reaction of lithium N-phenyl-N-methylcarbamate by quenching with deuterium oxide resulted in 87% formation of ortho deuterated N-methylaniline as estimated by ^{1}H NMR as shown in Table 1. No deuteration was observed at the N-methyl group.

Table 1. D-Incorporation of ortho-Carbon Atom of N-Methylaniline

Run	Solvent	Temp(°C)	Time(h)	Yield(%)[a]
1	THF	0	0.5	60
2	THF	0	2	80
3	THF	-70	1	38
4	THF	-20	1	82
5	THF/Et_2O(1:1)	-20	0.5	84
6	THF/Et_2O(1:4)	-20	0.5	87

a) D-Incorporation Yield by ^{1}H NMR



We now describe a novel one-pot synthetic sequence 1 to 7 for the regiospecific ortho-functionalization of N-methyl- and N-ethyl-aniline as typical N-monoalkylanilines. The sequence can be divided into five operations:

(i) **Protection.** The N-alkylaniline (1) was converted into the corresponding lithium carbamate (3) by reaction with n-butyllithium in tetrahydrofuran (1 to 2), followed by quenching with carbon dioxide (2 to 3).

(ii) **Lithiation.** Lithiation of this lithium carbamate (3) was accomplished by the addition of 1.2 equivalents of t-butyllithium in tetrahydrofuran or diethyl ether-tetrahydrofuran mixed solvent at ca. -20°C to give 4.

(iii) **Carbon-Carbon bond formation.** Intermediate 4 was converted to 5 by adding 1.1 equivalent of the electrophile at ca. -70°C and then allowing the mixture to rise to 25°C over a few hours.

(iv) **Deprotection.** Aqueous 2N hydrochloric acid was slowly added to the mixture at 0°C and kept for a few minutes to convert 5 to 7 via 6.

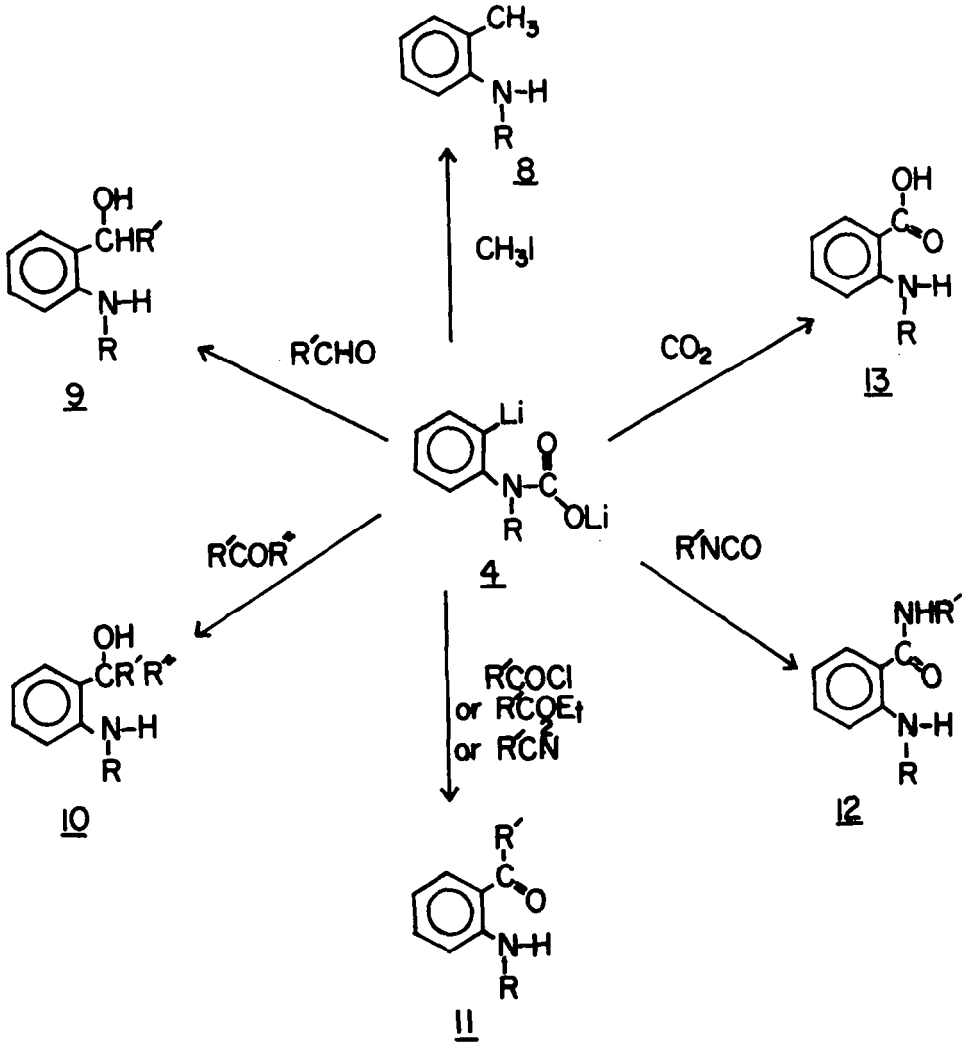


Table 2. Preparations of ortho-Substituted N-Methyl- and N-Ethyl-anilines

Entry	Starting Materials	Electrophiles	ortho-Substituent in Product	Yield(%)[a]	mp(°C)	lit.mp(°C)
1	PhNHMe	CH_3I	CH_3	64	206-208[b]	207-208[b,13]
2	PhNHMe	PhCHO	CH(OH)Ph	60	125-126	124-126[5]
3	PhNHMe	p-$O_2NC_6H_4CHO$	CH(OH)$C_6H_4NO_2$-p	48	126-127	127-128[5]
4	PhNHMe	Ph_2CO	$C(OH)Ph_2$	64	109-110	---
5	PhNHMe	CH_3COCH_3	$C(OH)(CH_3)_2$	55	74-76	75-78[5]
6	PhNHMe	PhCOCl	COPh	55	67-68	66-68[5]
7	PhNHMe	CO_2	CO_2H	71	174-179	178-179[14]
8	PhNHMe	PhNCO	CONHPh	69	124-125.5	122-123[15]
9	PhNHMe	tBuNCO	CONHtBu	71	165-166	---
10[c]	PhNHEt	CH_3I	CH_3	95[d]	214-215[b]	215[b,16]
11	PhNHEt	p-$CH_3OC_6H_4CHO$	CH(OH)$C_6H_4OCH_3$-p	84	92-93	---
12	PhNHEt	Ph_2CO	$C(OH)Ph_2$	74	108.5-109	---
13	PhNHEt	PhCOCl	COPh	51	34.5-35.5	35-36[17]
14	PhNHEt	$PhCO_2CH_3$	COPh	48	34.5-35.5	35-36[17]
15	PhNHEt	PhCN	COPh	35[e]	34.5-35.5	35-36[17]
16	PhNHEt	PhNCO	CONHPh	79	120.5-121	---
17	PhNHEt	tBuNCO	CONHtBu	75	109-110	---

a) Isolated Yield in all cases except Entry No 10

b) bp(°C)

c) N-Ethylaniline (10.0 ml, 79.5 mmole) was used as starting material.

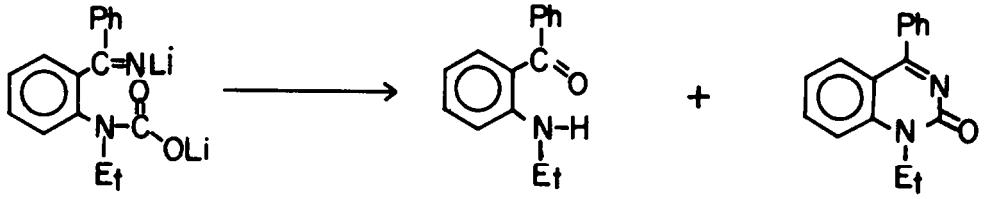
d) Yield by ^1H NMR after distillation

e) Quinazolinone (16) was isolated in 45 % yield.

(v) **Work-up.** The solution was made alkaline with aqueous sodium hydroxide at 0°C, extracted with chloroform twice, dried with anhydrous magnesium sulfate, the solvent removed, and the whole purified by distillation or recrystalization. This gave the corresponding ortho-substituted N-monoalkylaniline (4) in high yield.

The results are shown in Table 2.

A wide range of electrophiles was employed. In each case, with one exception, this gave a single product in yields of 48-95%. Groups introduced into the ortho-position include alkyl (from alkyl halides, cf 4 --> 8), secondary and tertiary alcohol (from aldehydes, 4 --> 9, and ketones, 4 --> 10 respectively), and ketones (from either esters or acid chlorides, 4 --> 11). Isocyanates and carbon dioxide as electrophiles give respectively o-carbonyl (4 --> 12) and o-carboxy derivatives (7 --> 13), as expected. The only case when a by product was formed was from benzonitrile (Table 2, entry 15), when in addition to 36% of the expected ketone (15) found by hydrolysis of an intermediate imine (14), the quinazolinone (16) was obtained in 45% yield.



14 15 16

In summary, ortho-substituted N-methyl- and N-ethyl-anilines were synthesized in one-pot sequences by the reaction of lithium N-phenyl-N-methyl- or N-phenyl-N-ethyl-carbamates with t-butyllithium as a key step. The particular ease of introduction and of removal which characterize our use of carbon dioxide as a protecting group offer considerable advantages over the N-substituents which have previously been applied for this purpose.

Interestingly, Gilman et al[18] attempted the dilithiation of aniline and N-n-butylaniline in 1940 but found that reaction with excess n-butylithium under reflux in diethyl ether for one to two days followed by treatment with carbon dioxide gave yields of only 4.2 and 2% respectively.

Experimental

General Melting points of the products were measured by a Thomas HOOVER Capillary Melting Point Apparatus and are uncorrected. IR spectra are of NaCl or KBr discs using a PERKIN-ELMER 283 B. ^{1}H NMR spectra were obtained with a Varian EM 360 L using tetramethylsilane as an internal standard. Elemental analyses were carried out under the supervision of Dr. R. King of this Department. Commercial N-methyl- and N-ethyl-anilines were dried over calcium hydride and used after distillation under dry argon. n-Butyllithium and t-butyllithium (Aldrich) were used without further purification. Tetrahydrofuran and diethyl ether, reagent grade from Fisher Chemical Co, were dried with calcium hydride and used directly after distillation under dry argon. Carbon dioxide (Matheson) was used after drying with anhydrous calcium sulfate. Electrophiles such as acetone and phenyl isocyanate were purified by standard methods before use.

Processes (i) to (iii) were carried out under dry argon.

Preparations of ortho-Substituted N-Methyl- and N-Ethyl-anilines

The interior of a Schlenk type reactor was flushed with argon. N-Ethylaniline (2.0 ml, 15.9 mmole) or N-methylaniline (1.73 ml, 15.9 mmole) was placed into the reactor. Tetrahydrofuran (50.0 ml) was added into the reactor. The resulting solution was cooled to ca -70°C and n-butyllithium (6.1 ml, 2.6 M n-hexane solution) was added dropwise. The solution was held at ca -70°C for a few minutes, allowed to rise to 25°C. Carbon dioxide gas was added to the solution for a few minutes. The solvent was evaporated under reduced pressure and pale yellow residue, lithium N-phenyl-N-ethylcarbamate, was obtained. The atmosphere was replaced by argon. Tetrahydrofuran (10.0 ml) and diethyl ether (30.0 ml) or tetrahydrofuran (50.0 ml) was added. The solution was cooled to ca -70°C. t-Butyllithium (11.0 ml, 1.7 M n-pentane solution) was added slowly, the color became bright yellow. The cooling bath was replaced to ice-salt bath, and solution was kept at ca -20°C for 30 to 60 minutes. The whole was cooled to ca -70°C and the electrophile (1.1 eq. mole) in tetrahydrofuran (8.0 ml) or diethylether (8.0 ml) was added. The reaction was allowed to regain room temperature over a few hours, and then aqueous hydrochloric acid (2 N) was added slowly at 0°C. Gas was evolved immediately. The solution was kept for a few minutes. The solution was neutralized and made alkaline by aqueous sodium hydroxide solution using ice, extracted with chloroform twice, washed with water, and dried with anhydrous magnesium sulfate. Evaporation of the solvent under reduced pressure gave the product. Purification was carried out by recrystalization or distillation.

N-Methyl-2-Methylaniline: C_7H_9N, ^1H NMR ($CDCl_3$) 2.13 (s, 3H, $-CH_3$), 2.90 (s,3H, $-NHCH_3$), 3.31 (s, 1H, -NHMe), 6.56-6.95, (m, 2H, ArC(4), and ArC(6)), and 7.00-7.45ppm (m, 2H, other aromatic protons).

2-Methyl-2(alpha-hydroxybenzyl)aniline: $C_{14}H_{15}NO$, ^1H NMR ($CDCl_3$) 2.77 (s, 3H, $-NHCH_3$), 3.50 (brs, 2H, -OH, and, -NHMe), 5.80 (s, 1H, -CH(OH)Ar), and 6.65-7.5ppm (m, 9H, aromatic protons).

N-Methyl-2-(alpha-hydroxyl-4-nitrobenzyl)aniline: $C_{14}H_{14}N_2O_3$, ^1H NMR ($CDCl_3$) 2.77 (s, 3H, $-NHCH_3$), 4.90 (s, 2H, -OH, and -NHMe), 5.95 (s, 1H, -CH(OH)Ar), 6.7-7.5ppm (m, 4H, aromatic protons), 7.6 (d, 2H, aromatic protons), and 8.3ppm (d, 2H, aromatic protons).

alpha-(2-Methylaminophenyl)-biphenylcarbinol: $C_{20}H_{19}NO$, ^1H NMR ($CDCl_3$) 2.57 (s, 3H, $-NHCH_3$), 4.50 (brs, 2H, -OH, -NHMe), 6.55-6.75 (m, 2H, aromatic protons), and 7.32ppm (m, 12H, aromatic protons); Elemental Analysis, Calcd. C, 83.04, H, 6.57, N, 4.84%; Found C, 82.84, H, 6.85, N, 4.60%.

2-(2-Methylamino)phenyl-2-propanol: $C_{10}H_{15}NO$, ^1H NMR ($CDCl_3$) 1.70 (s, 6H, $-C(OH)(CH_3)_2$), 2.88 (s, 3H, $-NHCH_3$), 3.65 (brs, 2H, -OH, and -NHMe), and 6.6-7.5ppm (m, 4H, aromatic protons).

2-Methylaminobenzophenone: $C_{14}H_{13}NO$, ^1H NMR ($CDCl_3$) 3.00 (d, 3H, $-NHCH_3$), 6.5-6.9 (m, 2H, ArC(3), and ArC(5)), 7.3-7.9(m, 7H, aromatic protons), and 8.6ppm (brs, 1H, -NHMe).

2-Methylaminobenzoic acid: C_8H_9NO, ^1H NMR ($CDCl_3$) 3.00 (s, 3H, $-NHCH_3$), 6.75 (d, 2H, aromatic protons), 7.55 (t, 1H, aromatic protons), 8.15 (d, 1H, aromatic protons), and 9.0ppm (brs, 2H, $-CO_2H$, and -NHMe).

N-Phenyl-2-methylaminobenzamide: $C_{14}H_{14}N_2O$, ^1H NMR ($CDCl_3$) 2.90 (s, 3H, $-NHCH_3$), and 6.55-7.9ppm (m, 11H, -NHPh, -NHMe, and aromatic protons).

N-(tert-Butyl)-2-methylaminobenzamide: $C_{12}H_{18}N_2O$, ^1H NMR ($CDCl_3$) 2.53 (s, 9H, $-C(CH_3)_3$), 2.85 (s, 3H, $-NHCH_3$), 5.90 (brs, 1H, -NHtBu), 6.73 (d, 2H, aromatic protons), and 7.35ppm (d, 3H, -NHMe, and aromatic protons), Elemental Analysis, Calcd. C, 69.90, H, 8.74, N, 13.60%; Found C, 69.53, H, 9.07, N, 13.26%.

2-Methyl-N-ethylaniline: $C_9H_{13}N$, ^1H NMR($CDCl_3$) 1.15 (t, 3H, J=7Hz, $-NHCH_2CH_3$), 3.06 (q, 2H, J=7Hz, $-NHCH_2CH_3$), 3.23 (s, 1H, -NHEt), 6.47-6.87 (m, 2H, ArC(4), and ArC(6)), and 6.95-7.37ppm (m, 2H, ArC(3), and ArC(5)).

N-Ethyl-2-(alpha-hydroxyl-4'-methoxybenzoyl)aniline: $C_{16}H_{19}NO_2$, ^1H NMR ($CDCl_3$) 1.10 (t, 3H, J=7Hz, $-NHCH_2CH_3$), 3.03 (q, 2H, J=7Hz, $-NHCH_2CH_3$), 3.67 (brs, 2H, -NHEt, and -OH), 3.80 (s, 3H, $-OCH_3$), 5.72 (s, 1H, -C(H)(OH)Ar), and 6.36-7.38ppm (m, 8H, aromatic protons), Elemental Analysis, Calcd. C, 74.68, H, 7.44,N, 5.44%; Found C, 74.74, H, 7.66, N, 5.24%.

alpha-(2-Methylaminophenyl)-biphenylmethanol: $C_{21}H_{21}NO$, ^1H NMR ($CDCl_3$) 0.92 (t, 3H, J=7Hz, $-NHCH_2CH_3$), 2.98 (q, 2H, J=7Hz, $-NHCH_2CH_3$), 4.52 (brs, 2H, -OH, and -NHEt), 6.57-6.88 (m, 2H, ArC(3), and ArC(5)), and 7.11-7.40ppm (m, 12H, ArC(4), ArC(6), and aromatic protons), Elemental Analysis; Calcd. C, 83.13, H, 6.98, N, 4.62%; Found C, 83.15, H, 7.38, N, 4.42%.

2-Ethylaminobenzophenone: $C_{15}H_{15}NO$, ^1H NMR ($CDCl_3$), 0.98 (t, 3H, J=7Hz, $-NHCH_2CH_3$), 3.05-3.50 (m, 2 H, $-NHCH_2CH_3$), 6.42-6.87 (m, 2H, ArC(3), and ArC(5)), 7.30-7.73 (m, 7H, other aromatic protons), and 8.63ppm (brs, 1H, -NHEt).

N-Phenyl-2-ethylaminobenzamide: $C_{15}H_{16}N_2O$, ^1H NMR ($CDCl_3$) 1.23 (brt, 3H, J=7Hz, $-NHCH_2CH_3$), 2.95-3.32 (brq, 2H, J=7Hz, $-NHCH_2CH_3$), 6.47-6.78 (m, 2H, ArC(3), and ArC(5)), 6.80-7.67 (m, 8H, -NHPh, other, aromatic protons) and 8.05ppm (brs, 1H, -NHEt), Elemental Analysis, Calcd. C, 74.97, H, 6.71, N, 11.66%; Found C, 74.92, H, 6.89, N, 11.50%;

N-t-Butyl-2-ethylaminobenzamide: $C_{13}H_{20}N_2O$, ^1H NMR ($CDCl_3$) 1.27 (brt, 3H, J=7Hz, $-NHCH_2CH_3$), 1.45 (s, 9H, $-C(CH_3)_3$), 3.20 (brq, 2H, J=7Hz, $-NHCH_2CH_3$), 5.95 (brs, 1H, -NHEt), 6.47-6.78 (m, 2H, ArC(3), and ArC(5)), and 7.22-7.45 (m, 3H, ArC(4), ArC(6), and -NHtBu), Elemental Analysis, Calcd. C, 70.87, H, 9.15, N, 12.72%; Found C, 70.88, H, 9.46, N, 12.68%

1-Ethyl-4-phenyl-quinazoline-2-one: $C_{16}H_{14}N_2O$, ^1H NMR ($CDCl_3$) 1.45 (t, 3H, J=7Hz, $-NHCH_2CH_3$), 4.43 (q, 2H, J=7Hz, $-NHCH_2CH_3$), and 7.13-8.17ppm (m, 9H, aromatic protons), Elemental Analysis, Calcd. C, 76.78, H, 5.64, N, 11.19%; Found C, 76.77, H, 5.83, N, 11.05%.

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