One-Pot Synthesis of Isothiachromene, Isochromene, Isoquinoline and Tetrahydronaphthalene Derivatives

A. M. El-Sayed* and H. Abdel-Ghany

Chemistry Department, Faculty of Science, Sohag, Egypt

Received October 1, 1999

A new series of tetrahydronaphthalene, isothiachromene, isochromene and isoquinoline derivatives were synthesized by reacting cyclohexylidenemalononitrile with active nitriles, active halo compounds, carbon disulfide, aldehydes, isothiocyanates and isocyanates, respectively.

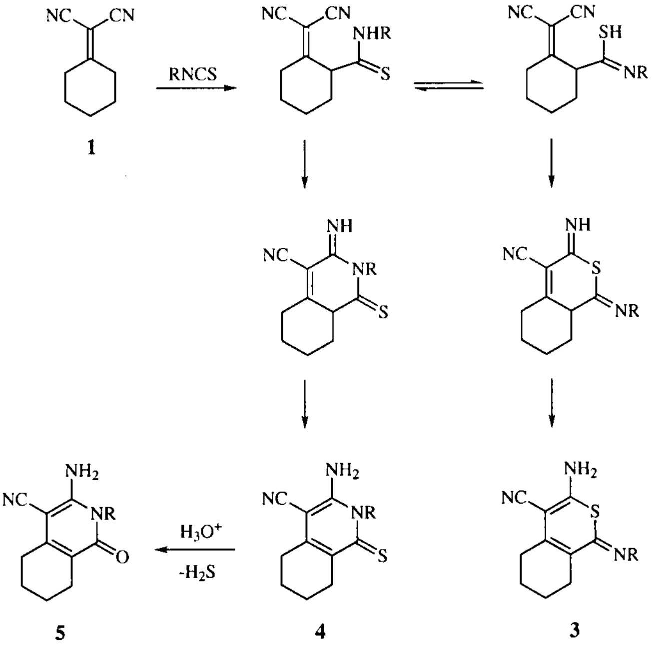
J. Heterocyclic Chem., **37**, 1233 (2000).

α, β-Unsaturated nitriles are versatile reagents which have been extensively utilized in heterocyclic synthesis [1-4]. Elgemeie [5-7] studied the reaction between cyclohexylidenemalononitrile and arylidenecyanoacetamide. Also El-Shafei [8] reported the synthesis of some spiro heterocycles from the reaction of cycloalkylidenemalononitriles with active methylene reagents. In this contribution the reaction of cyclohexylidenemalononitrile with isothiocyanates, isocyanates, carbon disulfide, active nitriles and active halo compounds have been investigated in a one-pot reaction under phase-transfer catalysis conditions to afford new series of isothiachromene, isochromene, isoquinoline and tetrahydronaphthalene derivatives.

The application of phase-transfer catalysis in carbanionic reactions provides one of the most important methods of organic synthesis because it simplifies procedures, eliminates expensive, inconvenient and dangerous reactants and solvents. Phase-transfer catalysis has been the subject of review articles [9-11], but only two deal with the chemistry of heterocyclic compounds [12,13].

Cyclohexylidenemalononitrile [14] **1** was allowed to react with carbon disulfide using solid-liquid phase-transfer catalysis techniques [benzene/potassium carbonate/-tetrabutylammonium bromide] to give the corresponding 3-amino-4-cyano-1-thioxo-5,6,7,8-tetrahydroisothiachromene (**2**). It has been reported [15] that the reaction of compound **1** with phenylisothiocyanate or phenylisocyanate in dimethylformamide using triethylamine as a catalyst affords 3-amino-4-cyano-2-phenyl-1-thioxo-5,6,7,8-tetrahydroisoquinoline (**4a**) or 3-amino-4-cyano-2-phenyl-5,6,7,8-tetrahydroisoquinolin-1-one (**5a**). We report here the reaction of compound **1** with phenylisothiocyanate under phase-transfer catalysis conditions gave 3-amino-4-cyano-1-phenylimino-5,6,7,8-tetrahydroisothiachromene (**3a**), 3-amino-4-cyano-2-phenyl-1-thioxo-5,6,7,8-tetrahydroisoquinoline (**4a**) and 3-amino-4-cyano-2-phenyl-5,6,7,8-tetrahydroisoquinolin-1-one (**5a**), in 1:1.75:1.65 ratio while the reaction of compound **1** with benzoylisothiocyanate under the same experimental conditions afforded 3-amino-2-benzoyl-4-cyano-1-thioxo-5,6,7,8-tetrahydroisoquinoline (**4b**) and 3-amino-2-benzoyl-4-cyano-5,6,7,8-tetrahydroisoquinolin-1-one (**5b**) in 1.06:1 ratio, but the reaction of compound **1** with ethyl isothiocyanate using the phase-transfer catalysis technique yielded 3-amino-4-cyano-1-ethylimino-5,6,7,8-tetrahydroisothiachromene (**3b**), and 3-amino-4-cyano-2-ethyl-5,6,7,8-tetrahydroisoquinolin-1-one (**5c**) in 1.23:1 ratio (see Scheme I, Table 1). The reaction pathway was suggested to proceed *via* addition of the active methylene group of compound **1** to the isothiocyanate followed by either the attack of the mercapto group to the cyano group yielding compounds **3a,b** or the attack of the imino group to the nitrile group to give compounds **4a,b** which are adsorbed on potassium carbonate and on acidifying the potassium carbonate solution with dilute hydrochloric acid, hydrogen sulfide was evolved with precipitation of compounds **5a-c** (see Scheme A).

Scheme A

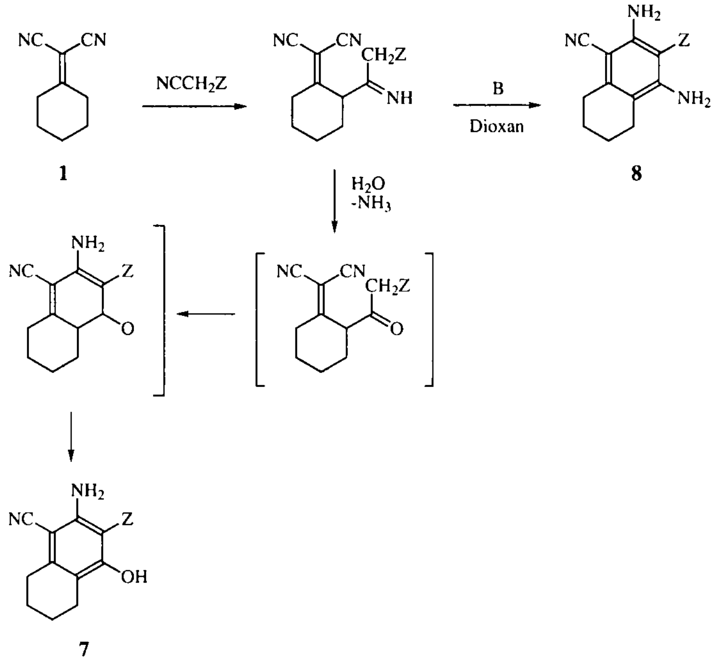


In analogy with isothiocyanates, the reaction of phenylisocyanate afforded 3-amino-4-cyano-1-phenylimino-5,6,7,8-

tetrahydroisochromene (**6**) (absorbed on potassium carbonate) and 3-amino-4-cyano-2-phenyl-5,6,7,8-tetrahydroisoquinolin-1-one (**5a**) (from acidified carbonate solution).

The reaction of active nitriles, including malononitrile and ethyl cyanoacetate, with the cyclohexylidenemalononitrile **1** gave 1-tetrahydronaphthylamines **8a,b** when the reaction was carried out in dioxan, but 1-tetrahydronaphthols **7a,b** were obtained on using ethanol (95%) as a solvent. The reaction mechanism was assumed to follow preliminary formation of a carbanion of the active methylene of compound **1** followed by nucleophilic attack to the cyano group of the active nitrile compounds, this imino intermediate underwent intramolecular cyclization through the addition of the methylene to the cyano group to give compounds **8a,b** when using dioxan as a solvent, while in ethanol solvent the imino group of the intermediate underwent hydrolysis to carbonyl group with evolution of ammonia (see Scheme B).

Scheme B



Treating compound **1** with benzoyl cyanide [16] gave 2-benzoylcyclohexylidenemalononitrile as an intermediate which cyclized to compound **9** (see Scheme I, Table 1).

The reaction between compound **1** and aromatic aldehydes in refluxing ethanol in presence of sodium acetate does not give the corresponding arylidene derivatives but affords compounds containing amino and cyano groups which were identified as 3-amino-4-cyano-1-phenyl-5,6,7,8-tetrahydroisochromene (**10a**), 3-amino-4-cyano-1-(*p*-methoxyphenyl)-5,6,7,8-tetrahydroisochromene (**10b**) and 3-amino-4-cyano-1-(*p*-nitrophenyl)-5,6,7,8-tetrahydroisochromene (**10c**) (see Scheme I, Table 1). The formation of these compounds was assumed to proceed *via* formation of an aldol adduct intermediate followed by cyclization. The obtained product **10a** was not the same as that obtained from the reaction of cyclohexanone with benzylidenemalononitrile under the same conditions as evidenced by its mp and spectral data, that is the formation of compounds **10a-c** does not proceed *via* arylidenemalononitrile and cyclohexanone intermediates.

On refluxing formaldehyde with compound **1** in ethanol for 5 hours in presence of triethylamine as a catalyst, 3-amino-4-cyano-5,6,7,8-tetrahydroisochromene (**11**) was obtained. While treatment of compound **1** with 2-(1-acetyl-2-oxopropylidene)benzoxazole yielded the corresponding spiro compound **12** (see Scheme I, Table 1).

Thioacetals are versatile reagents which have been extensively utilized in heterocyclic synthesis [17-21]. This prompted us to synthesize 2-dimethylthiomethylenecyclohexylidenemalononitrile (**13**) by reacting compound **1** with carbon disulfide and methyl iodide in 1:1:2 molar ratio under phase-transfer catalysis condition, which is similar in structure to a thioacetal. On refluxing compound **13** with an equimolar amount of aniline or hydrazine in 1:2 molar ratio in acetonitrile, 4-cyano-3-imino-1-methylthio-2-phenyl-5,6,7,8-tetrahydroisoquinoline (**14**) or 2-amino-4-cyano-1-hydrazino-3-imino-5,6,7,8-tetrahydroisoquinoline (**15**) respectively was formed (see Scheme I, Table 1).

3-Acetyl-1-cyano-4-methylthio-5,6,7,8-tetrahydro-2-naphthylamine (**16**) was obtained by refluxing compound **1** with 3-[di(methylthio)methylene]pentan-2,4-dione in ethanol in presence of triethylamine catalyst (see Scheme I, Table 1).

Indene derivatives **18a-c** were prepared by reacting compound **1** with active halo compounds, namely, phenacyl bromide, chloroacetonitrile or chloroacetaldehyde under phase-transfer catalysis conditions (see Scheme I, Table 1). The reaction mechanism follows firstly alkylation of compound **1** at the 2-position followed by addition of the methylene group to the cyano group to give the cyclized compound. This mechanism was confirmed by separating the intermediate **17** from the reaction of compound **1** with phenacyl bromide using phase-transfer catalysis technique, as well as by applying the phase-transfer catalysis technique on this compound at a higher temperature and with a longer reaction time to yield compound **18a**.

The reaction of 1,3-dibromopropane with compound **1** under phase-transfer catalysis conditions gave 1-cyano-3,4,5,6,7,8-hexahydronaphthalene (**19**) (see Scheme I, Table 1).

Treatment of compound **1** with chloroacetyl chloride in pyridine afforded 3-amino-2-chloro-4-cyano-5,6,7,8-tetrahydro-1-naphthol (**20**) (see Scheme I, Table 1). The reaction mechanism was assumed to proceed through chloroacetylation of compound **1** at the 2-position followed by the addition of the methylene group to the cyano group to yield the cyclized product.

Table I

Analytical and Spectral Data of the Prepared Compounds

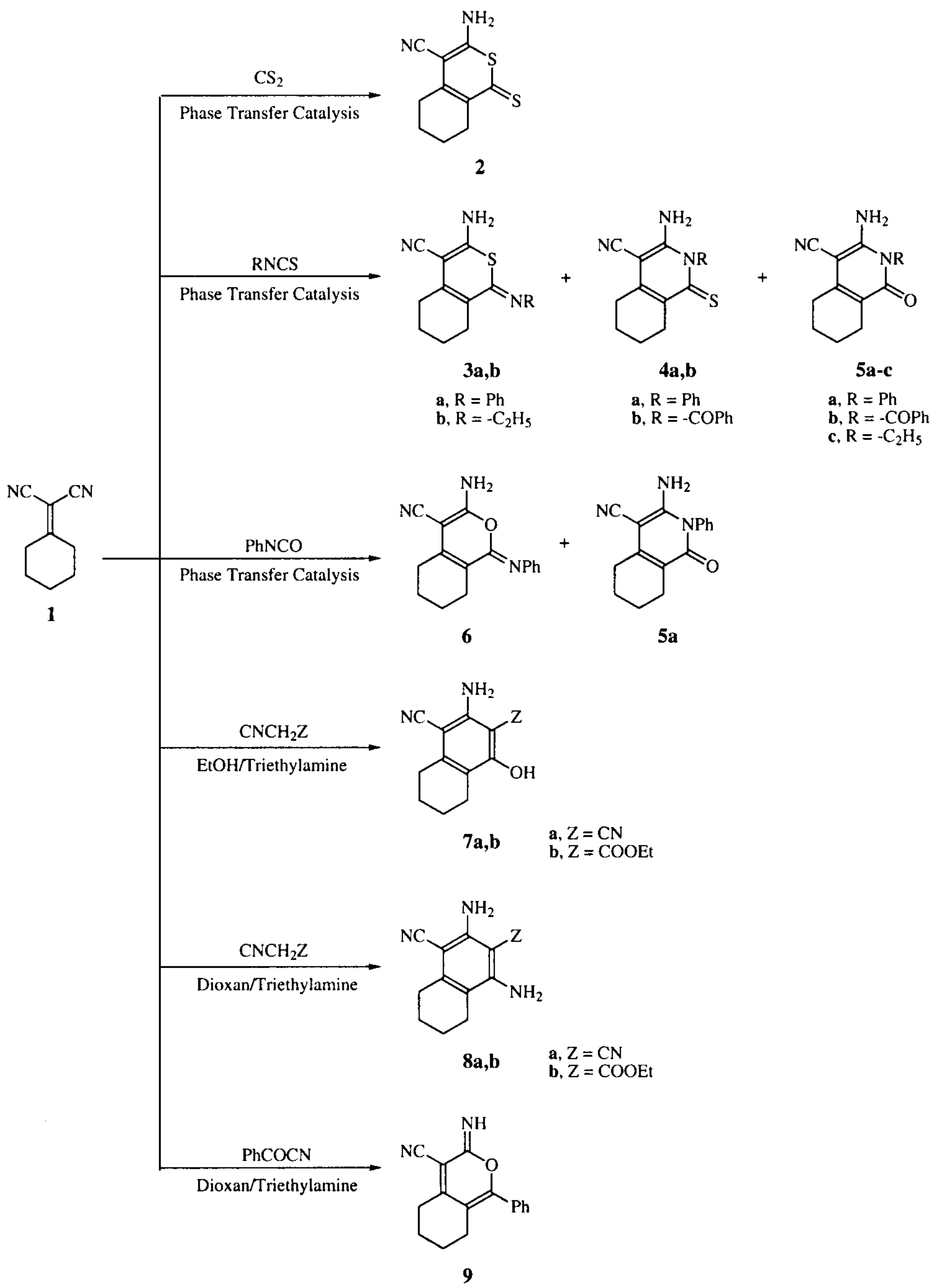
Compound No.	Reaction time (h) Reaction temp. (°C)	MP [a] °C (cryst. Solv.)	Yield (%)	Moecular. Form (Molecular wt.)	Analytical Data[b] Calcd./Found C	H	N	IR (KBr) [c] ν (cm^{-1})	H-NMR (DMSO-d$_6$) [d] δ (ppm)
2	5/25	253 (methanol)	82	$C_{10}H_{10}N_2S_2$ (222.33)	54.02 54.30	4.53 4.45	12.60 12.42	3296, 3181 (NH$_2$); 2208 (CN); 1325 (CS)	3.80 (s, 2H, NH$_2$); 2.80-2.40 (m, 4H, 2CH$_2$); 1.90-1.45 (m, 4H, 2CH$_2$).
3a	5/60	262 (methanol)	20	$C_{16}H_{15}N_3S$ (281.38)	68.30 68.24	5.37 5.31	14.93 14.86	3327, 3223 (NH$_2$); 2206 (CN)	7.90-7.15 (m, 5H, arom.); 4.95 (s, 2H, NH$_2$); 290-2.50 (m, 4H, 2CH$_2$); 2.10-1.65 (m, 4H, 2CH$_2$).
3b	6/70	132 (ethanol)	37	$C_{12}H_{15}N_3S$ (233.34)	61.77 61.70	6.48 6.28	18.01 18.19	3335, 3215 (NH$_2$); 2210 (CN)	4.75 (s, 2H, NH$_2$); 3.40-3.15 (q, 2H, CH$_2$); 2.85-2.40 (m, 4H, 2CH$_2$); 2.15-1.70 (m, 4H, 2CH$_2$); 1.20-0.95 (t, 3H, CH$_3$).
4a	5/60	270 [e] (benzene)	35	$C_{16}H_{15}N_3S$ (281.38)	68.30 68.02	5.37 5.08	14.93 14.73	3338, 3225 (NH$_2$); 2207 (CN) 1133 (CS)	7.70-7.10 (m, 5H, arom); 4.90 (s, 2H, NH$_2$); 2.90-2.45 (m, 4H, 2CH$_2$); 1.90-1.40 (m,4H, 2CH$_2$).
4b	5/25	194 (ethanol)	34	$C_{17}H_{15}N_3OS$ (309.39)	66.00 65.92	4.89 4.77	13.58 13.62	3342, 3230 (NH$_2$); 2199 (CN) 1701 (CO); 1128 (CS).	7.90-7.35 (m, 5H, arom); 5.05 (s, 2H, NH$_2$); 3.05-2.50 (m, 4H, 2CH$_2$); 1.95-1.45 (m, 4H, 2CH$_2$).
5a	5/60	278 [f] (dioxan)	33	$C_{16}H_{15}N_3O$ (265.32)	72.43 72.40	5.70 5.58	15.84 15.65	3352, 3237 (NH$_2$); 2206 (CN), 1655 (CO).	7.65-7.40 (m, 5H, arom); 4.2 (s, 2H, NH$_2$); 2.95-2.50 (m, 4H, 2CH$_2$); 1.90-1.50 (m, 4H, 2CH$_2$).
5b	5/25	148 (dioxan)	32	$C_{17}H_{15}N_3O_2$ (293.33)	69.61 69.66	5.15 5.19	14.33 14.25	3337, 3221 (NH$_2$); 2209 (CN) 1702 1697 (2CO).	7.85-7.30 (m, 5H, arom); 5.40(s, 2H, NH$_2$); 2.90-2.50 (m, 4H, 2CH$_2$); 1.95-1.45 (m,4H, 2CH$_2$).
5c	6/70	164 (ethanol)	30	$C_{12}H_{15}N_3O$ (217.27)	66.34 66.05	6.96 6.90	19.34 19.50	3350, 3230 (NH$_2$); 2208 (CN) 1700 (CO).	4.90 (s, 2H, NH$_2$); 3.65-3.20 (q, 2H, CH$_2$); 2.85-2.45 (m, 4H, 2CH$_2$); 1.95-1.40 (m, 4H, 2CH$_2$); 1.10-0.90 (t, 3H, CH$_3$).
6	6/70	234 (methanol)	39	$C_{16}H_{15}N_3O$ (265.32)	72.43 72.28	5.70 5.75	15.84 15.91	3318, 3198 (NH$_2$); 2199 (CN).	7.75-7.20 (m, 5H, arom); 5.15 (s, 2H, NH$_2$); 2.90-2.40 (m, 4H, 2CH$_2$); 1.90-1.40 (m,4H, 2CH$_2$).
7a	5/reflux	>300 (ethanol)	67	$C_{12}H_{11}N_3O$ (213.24)	67.59 67.65	5.20 5.08	19.71 19.88	3461 (OH); 3352, 3229 (NH$_2$); 2227, 2209 (2CN).	5.60 (s, 2H, NH$_2$); 2.90-2.45 (m, 4H, 2CH$_2$); 1.85-1.45 (m,4H, 2CH$_2$).
7b	7/reflux	138 (benzene/ pet. ether 40-60	62	$C_{14}H_{16}N_2O_3$ (260.30)	64.60 64.50	6.20 6.12	10.76 10.70	3459 (OH); 3341, 3221 (NH$_2$); 2203 (CN)' 1735 (CO).	5.35 (s, 2H, NH$_2$); 4.45-4.05 (q, 2H, CH$_2$); 2.80-2.35 (m,4H, 2CH$_2$); 1.90-1.45 (m, 2H, 2CH$_2$); 1.25-0.90 (t, 3H, CH$_3$).
8a	1/reflux	181 dioxan	54	$C_{12}H_{12}N_4$ (212.26)	67.90 67.68	5.70 5.79	26.40 26.48	3435,3323, 3219 (2NH$_2$), 2201, 2197 (2CN).	5.75 (s, 2H, NH$_2$); 5.15 (s, 2H, NH$_2$); 2.65-2.25 (m, 4H, 2CH$_2$); 1.85-1.50 (m, 4H, 2CH$_2$).
8b	2/reflux	107 (penzene/ pet. ether 40-60	51	$C_{14}H_{17}N_3O_2$ (259.31)	64.85 64.80	6.61 6.65	16.20 16.29	3431, 3337, 3225 (2NH$_2$), 2208 (CN); 1733 (CO).	5.55 (s, 2H, NH$_2$), 4.95 (s, 2H, NH$_2$); 4.50-4.15 (q, 2H, CH$_2$); 2.75-2.40 (m, 4H, 2CH$_2$); 1.90-1.55 (m, 4H, 2CH$_2$); 1.30-0.95 (t, 3H, CH$_3$)
9	2/25	>300 methanol	78	$C_{16}H_{14}N_2O$ (250.30)	76.78 76.69	5.64 5.70	11.19 11.01	3311 (NH); 2220 (CN).	9.55 (s, 1H, NH); 7.65-7.30 (m, 5H, arom.); 2.85-2.50 (m, 4H, 2CH$_2$); 1.85-1.55 (m, 4H, 2CH$_2$).

Table I (continued)

10a	4/reflux	265 methanol	55	$C_{16}H_{16}N_2O$ (252.32)	76.16 76.00	6.39 6.43	11.10 10.93	3341, 3242 (NH_2); 2208 (CN).	7.70-7.15 (m, 5H, arom.); 6.65 (s, 2H, NH_2); 5.70 (s, 1H, CH); 2.85-2.45 (m, 4H, $2CH_2$); 1.90-1.55 (m, 4H, $2CH_2$).
10b	3/reflux	249 methanol	58	$C_{17}H_{18}N_2O_2$ (282.35)	72.32 72.02	6.43 6.52	9.92 9.86	3347, 3237 (NH_2); 2212 (CN).	7.65-6.95 (m, 4H, arom.); 5.95 (s, 2H, NH_2); 4.70 (s, 1H, CH); 3.80 (s, 3H, OCH_3); 2.45-2.05 (m, 4H, $2CH_2$); 1.85-1.40 (m, 4H, $2CH_2$).
10c	2/reflux	154 methanol	54	$C_{16}H_{15}N_3O_3$ (297.32)	64.64 64.50	5.09 5.16	14.13 14.00	3347, 3237 (NH_2); 2208 (CN); 1520, 1344 (NO_2).	8.55-7.40 (m, 4H, arom.); 5.80 (s, 2H, NH_2); 4.85 (s, 1H, CH); 2.40-2.10 (m, 4H, $2CH_2$); 1.90-1.55 (m, 4H, $2CH_2$).
11	5/reflux	140 aq.methanol	82	$C_{10}H_{12}N_2O$ (176.22)	68.16 68.30	6.86 6.79	15.90 15.80	3351, 3231 (NH_2); 2198 (CN).	5.25 (s, 2H, NH_2); 3.75 (s, 2H, CH_2); 2.35-2.10 (m, 4H, $2CH_2$); 1.85-1.50 (m, 4H, $2CH_2$).
12	7/reflux	132 chloroform	47	$C_{19}H_{18}N_3O_2$ (320.37)	71.23 71.30	5.66 5.60	13.12 12.93	3438, 3354, 3225 (NH, NH_2); 2197 (CN); 1675 (CO).	12.60 (s, 1H, NH); 7.35-6.45 (m, 4H, arom.); 5.85 (s, 2H, NH_2); 3.80 (t, 1H, CH); 3.45 (s, 3H, CH_3); 2.45 (t, 2H, CH_2); 1.90-1.30 (m, 6H, $3CH_2$).
13	2/60	172 benzene/ pet . ether 60-80°	82	$C_{12}H_{14}N_2S_2$ (250.39)	57.56 57.48	5.64 5.72	11.19 11.05	2199 (CN).	3.10 (s, 6H, $2CH_3$); 2.85-2.40 (m, 4H, $2CH_2$); 1.95-1.45 (m, 4H, $2CH_2$).
14	2/25	276 dioxan	77	$C_{17}H_{17}N_3S$ (295.41)	69.12 69.00	5.80 5.88	14.22 14.05	3414 (NH); 2209 (CN).	9.55 (s,1H,NH); 7.55-6.65 (m, 5H, arom.); 3.05 (s, 3H, CH_3); 2.75-2.30 (m, 4H, $2CH_2$); 1.85-1.50 (m, 4H, $2CH_2$).
15	22/reflux	>300 dioxan	75	$C_{10}H_{14}N_6$ (218.26)	55.03 55.20	6.47 6.40	38.50 38.62	3415, 3316, 3251, 3201 (2NH, $2NH_2$); 2199 (CN).	10.35 (s, 1H, NH); 9.85 (s, 1H, NH); 6.35 (b, 4H, $2NH_2$); 2.80-2.35 (m, 4H, $2CH_2$); 1.90-1.55 (m, 4H, $2CH_2$).
16	15/reflux	127 methanol	66	$C_{14}H_{162}OS$ (260.36)	64.59 64.46	6.19 6.25	10.76 10.64	3346, 3234 (NH_2); 2199 (CN); 1701.	4.95 (s, 2H, NH_2); 3.20 (s, 3H, CH_3); 3.00 (s, 3H, CH_3); 2.85-2.35 (m, 4H, $2CH_2$); 1.85-1.50 (m, 4H, $2CH_2$).
17	25/reflux	117 benzene/ pet. ether 40-60°	92	$C_{17}H_{16}N_2O$ (264.33)	77.25 77.00	6.10 6.22	10.60 10.53	2221 (CN); 1699 (CO).	8.10-7.35 (m, 5H, arom.), 3.60-3.75 (d, 2H, CH_2); 2.60-2.15 (m, 5H, $CH+2CH_2$); 1.85-1.50 (m, 4H, $2CH_2$).
18a	3/25	165 methanol	83	$C_{17}H_{16}N_2O$ (264.33)	77.25 76.95	6.10 6.23	10.60 10.42	3345, 3329 (NH_2); 2210 (CN); 1701 (CO).	7.85-7.15 (m, 5H, arom.); 4.55 (s, 2H, NH_2); 2.85-2.30 (m, 5H, $CH+2CH_2$); 1.85-1.45 (m, 4H, $2CH_2$).
18b	7/80	272 methanol	90	$C_{11}H_{11}N_3$ (185.23)	71.32 71.02	5.99 6.09	22.69 22.60	3351, 3227 (NH_2); 2201, 2198 (2CN).	4.35 (s, 2H, NH_2); 2.95-2.35 (m, 5H, $CH+2CH_2$); 1.85-1.20 (m, 4H, $2CH_2$).
18c	4/80	123 benzene	69	$C_{11}H_{12}N_2O$ (188.23)	70.19 70.30	6.43 6.38	14.88 14.69	3359, 3229 (NH_2); 2203 (CN), 1710 (CO).	9.35 (s, 1H, CHO); 4.55 (s, 2H, NH_2); 2.90-2.20 (m, 5H, $CH+ 2CH_2$); 1.85-1.35 (m, 4H, $2CH_2$).
19	6/80	99 methanol	85	$C_{11}H_{13}N$ (159.23)	82.98 82.72	8.23 8.32	8.80 8.65	2195 (CN).	2.90-2.15 (m, 8H, 4CH2); 1.85-1.35 (m, 4H, $2CH_2$).
20	2/25- 4/reflux	>300 (methanol)	54	$C_{11}H_{11}ClN_2O$ (222.68)	59.33 59.08	4.98 5.10	12.58 12.43	3469 (OH); 3339, 3221 (NH_2); 2214 (CN).	4.95 (s, 2H, NH_2); 3.35-3.15 (s, 1H, OH); 2.95-2.30 (m, 4H, $2CH_2$); 1.95-1.35 (m, 4H, $2CH_2$).

[a] Uncorrected. [b] Satisfactory microanalysis obtained C, ± 0.35%; H, ± 0.20%; N, ± 0.20%. [c] Measured on Nicolet 710 FT-IR spectrophotometer. [d] Measured with a varian EM 360 L using TMS as internal standard. [e] Lit. Mp 269-270° ref. [15]. [f] Lit. Mp 278° ref. [15].

Scheme 1



EXPERIMENTAL

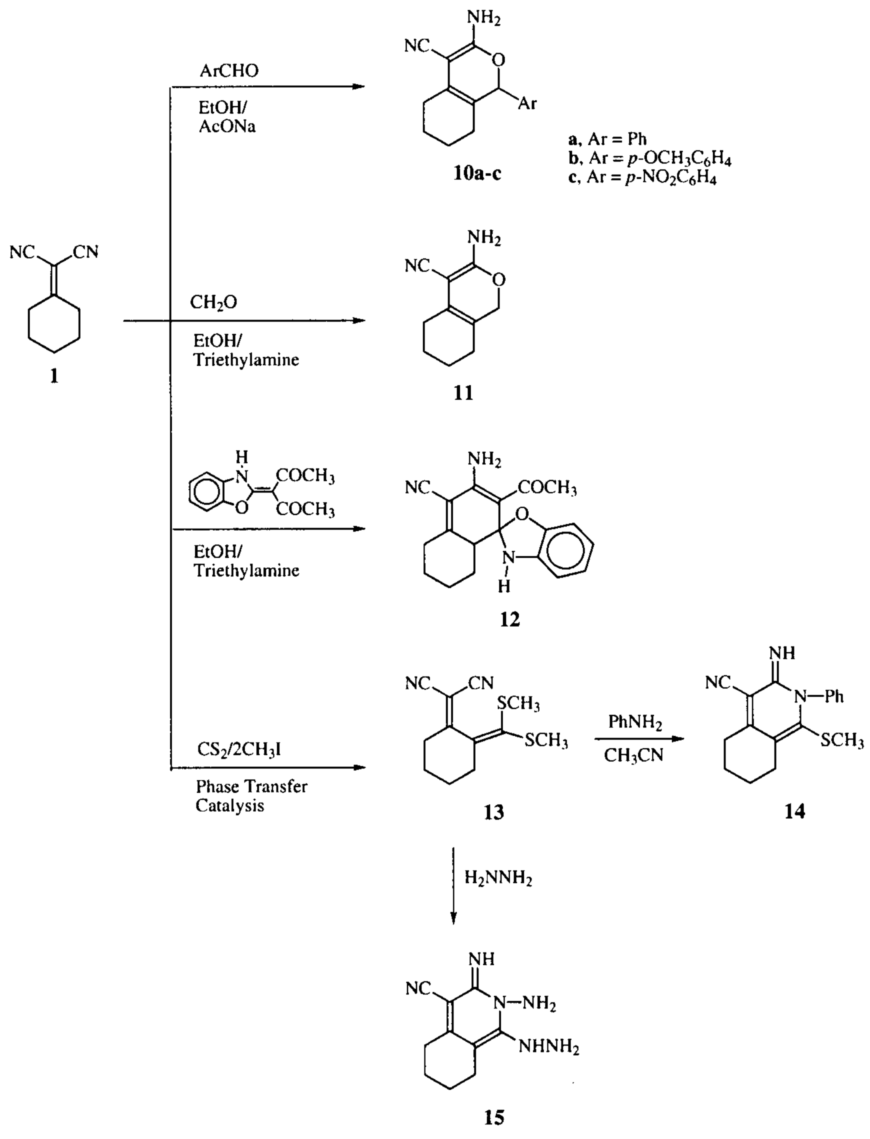
All ^{13}C-NMR spectra were determined using a Brucker AM 300 NIH$_3$ instrument.

Synthesis of 3-amino-4-cyano-1-thioxo-5,6,7,8-tetrahydroisothiachromene (**2**); 3-amino-4-cyano-1-phenyl(ethyl)imino-5,6,7,8-tetrahydroisothiachromene (**3a,b**); 3-amino-4-cyano-2-phenyl(benzoyl)-1-thioxo-5,6,7,8-tetrahydroisoquinoline (**4a,b**); 3-amino-4-cyano-2-phenyl(benzoyl,ethyl)-5,6,7,8-tetrahydroisoquinolin-1-one (**5a-c**) and 3-amino-4-cyano-1-phenylimino-5,6,7,8-tetrahydroisochromene (**6**).

General Procedure.

To a mixture of anhydrous potassium carbonate (3 g), dry benzene (40 ml), compound **1** (0.01 mol) and a catalytic amount of tetrabutylammonium bromide (0.5 mmol) was added an equimolar amount of carbon disulfide, phenylisothiocyanate, benzoylisothiocyanate, ethylisothiocyanate or phenylisocyanate. The reaction mixtures were stirred over different periods of time at different temperatures, (see Table I) till the com-

Scheme I (continued)



pletion of the reaction (thin layer chromatography). The reaction mixtures were filtered, the filtrate was washed thoroughly with water dried over anhydrous magnasium sulfate and evaporated *in vacuo*. The solid residue was crystallized from the proper solvent where compound **3a,b** were obtained. The solid potassium carbonate was dissolved in distilled water (50 ml). The separated solid was collected by filtration and crystallized from a suitable solvent where compounds **4a,b** and **6** were obtained. The filtrate (carbonate solution) was acidified with dilute hydrochloric acid where compounds **5a-c** were separated, collected by filtration and crystallized from the proper solvent (see Table I, Scheme 1).

3-Amino-4-cyano-1-ethylimino-5,6,7,8-tetrahydroisothiachromene (**3b**).

The following ^{13}C NMR resonances were observed (dimethyl sulfoxide-d$_6$, δ ppm): 12.19, 24.17, 25.61, 25.82, 48.26, 99.13, 99.56, 113.95, 115.43, 118.72, 129.67.

3-Amino-2-benzoyl-4-cyano-5,6,7,8-tetrahydroisochromene (**5b**).

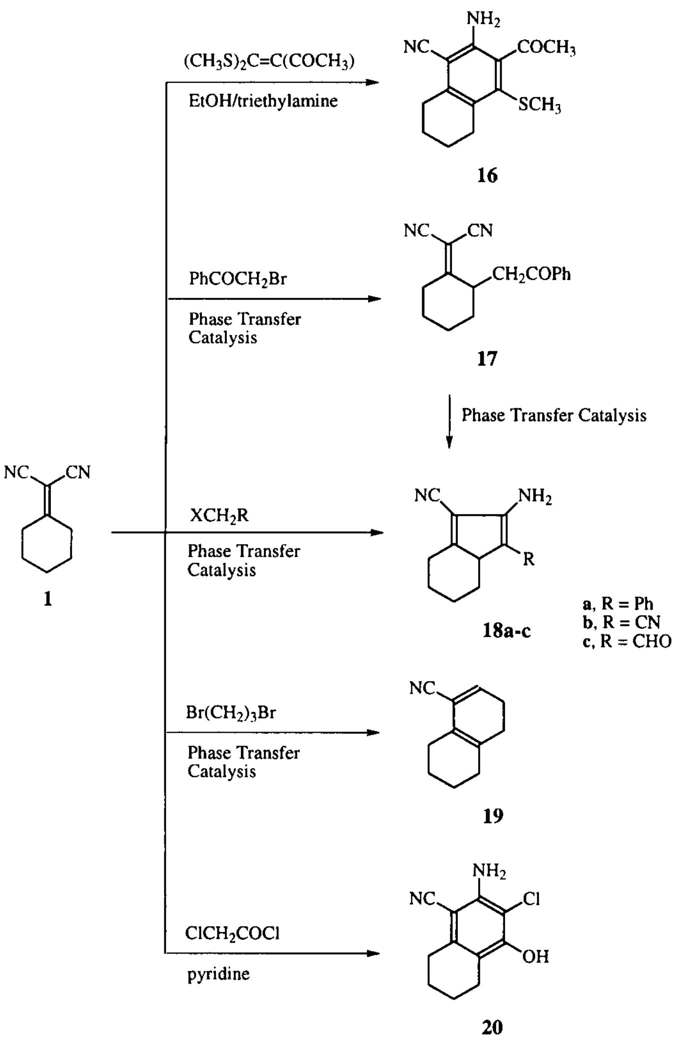
The following ^{13}C NMR resonances were observed (dimethyl sulfoxide-d$_6$, δ ppm): 24.09, 24.51, 25.71, 25.89, 99.62, 101.32, 114.79, 115.31, 118.97, 127.71, 127.84, 129.23, 129.51, 132.15, 139.11, 153.14, 165.37.

Synthesis of 3-amino-4-cyano-3-substituted-5,6,7,8-tetrahydro-1-naphthol (**7a,b**) and 3-amino-4-cyano-3-substituted-5,6,7,8-tetrahydro-1-naphthyl-amine (**8a,b**).

General Procedure.

To a solution of compound **1** (0.01 mol) in ethanol 95% (25 ml) or dry dioxan (10 ml) and a catalytic amount of triethylamine (2 drops) was added an equimolar amount of malononitrile or ethyl cyanoacetate. The reaction mixture was refluxed for a period of time between 1-7 hours, concentrated and the separated solid was collected by filtration and crystallized from the proper solvent (see Table I, Scheme 1).

Scheme I (continued)



3-Amino-4-cyano-3-ethoxycarbonyl-5,6,7,8-tetrahydro-1-naphthol (**7b**).

The following ^{13}C NMR resonances were observed (dimethyl sulfoxide-d$_6$, δ ppm): 11.81, 23.96, 24.15, 24.61, 24.81, 52.27, 119.21, 123.81, 124.11, 125.63, 126.29, 127.14, 129.94, 171.39.

4-Cyano-3-imino-1-phenyl-5,6,7,8-tetrahydroisochromene (**9**).

A solution of compound **1** (0.01 mol), benzoyl cyanide (0.01 mol) and a catalytic amount of triethylamine (2 drops) in dry dioxan (15 ml) was stirred at room temperature for 2 hours, and left overnight. The precipitated solid was collected by filtration, washed with ethanol and crystallized from ethanol (see Table I, Scheme 1).

Synthesis of 3-amino-4-cyano-1-phenyl(*p*-methoxyphenyl, *p*-nitrophenyl)-5,6,7,8-tetrahydroisochromene (**10a-c**).

General Procedure.

To a solution of compound **1** (0.01 mol) and the proper aromatic aldehyde (0.01 mol) in absolute ethanol (25 ml) was added sodium acetate (2 g). The reaction mixture was refluxed for 2-7 hours. Sodium acetate was isolated by filtration. The filtrate was concentrated and the isolated solid was collected by filtration and crystallized from the proper solvent (see Table I, Scheme 1).

3-Amino-4-cyano-1-phenyl-5,6,7,8-tetrahydroisochromene (**10a**).

The following ^{13}C NMR resonances were observed (dimethyl sulfoxide-d$_6$, δ ppm): 24.40, 24.83, 25.56, 25.89, 78.48, 98.19, 99.20, 114.36, 115.16, 118.45, 120.19, 124.73, 127.21, 128.55, 128.98, 129.85.

3-Amino-4-cyano-5,6,7,8-tetrahydroisochromene (**11**).

A solution of compound **1** (0.01 mol) and formaline solution 30% (0.6 ml) in ethanol (20 ml) was treated with a few drops of triethylamine (2 drops). The reaction mixture was refluxed for 5 hours, concentrated and the separated solid was collected by filtration and crystallized, (see Table I); ^{13}C NMR (dimethyl sulfoxide-d$_6$, δ ppm): 24.39, 24.79, 25.18, 25.65, 58.74, 97.87, 99.57, 113.66, 115.25, 118.68.

2-Acetyl-3-amino-4-cyano-5,6,7,8-tetrahydronaphthalene-1-spiro-2'-2',3'-dihydrobenzoxazole (**12**).

Compound **1** (0.01 mol) along with an equimolar amount of 2-(1-acetyl-2-oxopropylidene)benzoxazole was dissolved in ethanol (25 ml). To the reaction mixture was added catalytic amount of triethylamine (2 drops). The reaction mixture was refluxed for 7 hours. The solvent was evaporated *in vacuo*. The residue was treated with chloroform/petroleum ether 40-60 and the separated solid was crystallized from chloroform (see Table I).

2-[2-(Bis-methylthiomethylene)-cyclohexylidene]-malononitrile (**13**).

Compound **1** (0.01 mol) along with 0.01 mole of carbon disulfide in benzene (50 ml) was treated with 3 g of anhydrous potassium carbonate and a catalytic amount of tetrabutylammonium bromide (0.5 mmol). The reaction mixture was stirred at 60° for 2 hours, cooled and methyl iodide (0.02 mol) was added. The reaction mixture was stirred at room temperature for 2 hours. The benzene layer was separated by filtration, washed thoroughly with water, dried over anhydrous magnasium sulfate and evaporated *in vacuo*. The solid residue was crystallized from petroleum ether 60-80/benzene (7:3) (see Table I).

Synthesis of 4-cyano-3-imino-1-methylthio-2-phenyl-5,6,7,8-tetrahydroisoquinoline (**14**) and 2-amino-4-cyano-1-hydrazino-3-imino-5,6,7,8-tetrahydroisoquinoline (**15**).

General Procedure.

Compound **13** (0.005 mol) was dissolved in acetonitrile (20 ml) and treated with an equimolar amount of aniline or hydrazine hydrate (0.01 mol). The reaction mixture was refluxed for 22 hours or 15 hours respectively. The reaction mixture was concentrated and cooled. The separated solid was collected by filtration and crystallized from the proper solvent (see Table I).

4-Cyano-3-imino-1-methylthio-2-phenyl-5,6,7,8-tetrahydroisoquinoline (**14**).

The following ^{13}C NMR resonances were observed (dimethyl sulfoxide-d$_6$, δ ppm): 22.33, 24.13, 24.68, 25.88, 26.19, 99.15, 99.85, 109.38, 116.15, 118.66, 123.17, 123.68, 128.13, 128.49, 134.26, 135.19, 142.14.

Synthesis of 3-acetyl-1-cyano-4-methylthio-5,6,7,8-tetrahydro-2-naphthylamine (**16**).

A mixture of compound **1** (0.005 mol), 3-[di(methylthio)methylene]pentan-2,4-dione (0.005 mol) and catalytic amount of triethylamine (2 drops) was refluxed in absolute ethanol (20 ml) for 24 hours. On cooling, the precipitate was filtered off and crystallized from ethanol (see Table I); ^{13}C NMR (dimethyl sulfoxide-d_6, δ ppm): 22.69, 23.11, 23.95, 24.12, 24.59, 24.86, 115.76, 119.13, 122.30, 123.21, 124.14, 125.16, 126.20, 156.33.

Synthesis of Compounds **17**, **18a-c** and **19**.

General Procedure.

A mixture of 3 g anhydrous potassium carbonate, compound **1** (0.01 mol), dry benzene (30 ml) and a catalytic amount of tetrabutylammonium bromide (0.5 mmol) was treated with 0.01 mole of phenacyl bromide, chloroacetonitrile, chloroacetaldehyde or 1,3-dibromopropane. The reaction mixtures were stirred for a period between 3-10 hours at different temperatures. The reaction mixtures were filtered, the filtrate washed with water, dried over anhydrous magnasium sulfate and evaporated *in vacuo*. The residue was triturated with petroleum ether to give a solid which was crystallized from the appropriate solvent (see Table I, Scheme 1).

The following ^{13}C NMR resonances of compound **18c** were observed (dimethyl sulfoxide-d_6, δ ppm): 23.81, 24.21, 24.45, 24.64, 24.94, 97.92, 115.13, 116.37, 116.63, 118.82, 186.44.

3-Amino-2-chloro-4-cyano-5,6,7,8-tetrahydro-1-naphthol (**20**).

To a solution of compound **1** (0.01 mol) in dry pyridine (20 ml) was added chloroacetyl chloride (0.01 mol) dropwise with stirring through 10 minutes. The reaction mixture was stirred at room temperature for an additional 2 hours and refluxed for 4 hours. The mixture was poured into ice-water and the separated solid was filtered off and crystallized from ethanol (see Table I).

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