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SYNTHESIS OF PYRROLE, PYRIDINONE AND PYRIMIDINONE DERIVATIVES USING PTC CONDITIONS

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Abstract: The reaction of anilinomethylenemalononitrile 1 or 1,4-di(malononitrilemethyleneamino)benzene 7 with some reactive halo compounds in a one-pot reaction under PTC conditions affords a new series of pyrrole and pyridinone compounds. The reaction of compounds 1 or 7 with ethyl chloroformate gives the corresponding esters which underwent cyclization on reaction with different amino compounds affording the pyrimidinone derivatives.

In connection with our previous work on the application of phase-transfer catalysis (PTC) in heterocyclic synthesis[1-6], we report here the reaction of anilinomethylenemalononitrile[7] 1 or 1,4-di(malononitrilemethyleneamino)benzene 7 with some reactive halo compounds in a one-pot reaction, under PTC conditions [K_2CO_3/ dioxane or dimethylformamide/tetrabutylammonium bromide (TBAB)]. The reaction of compound 1 with ethyl chloroacetate, chloroacetamide, phenacyl bromide or diethyl bromomalonate afford the corresponding pyrrole derivatives 2a-c and 3 (Scheme I). Compound 7 reacted with the same reagents in 1:2 molar ratio under the same experimental PTC conditions to afford the corresponding di-

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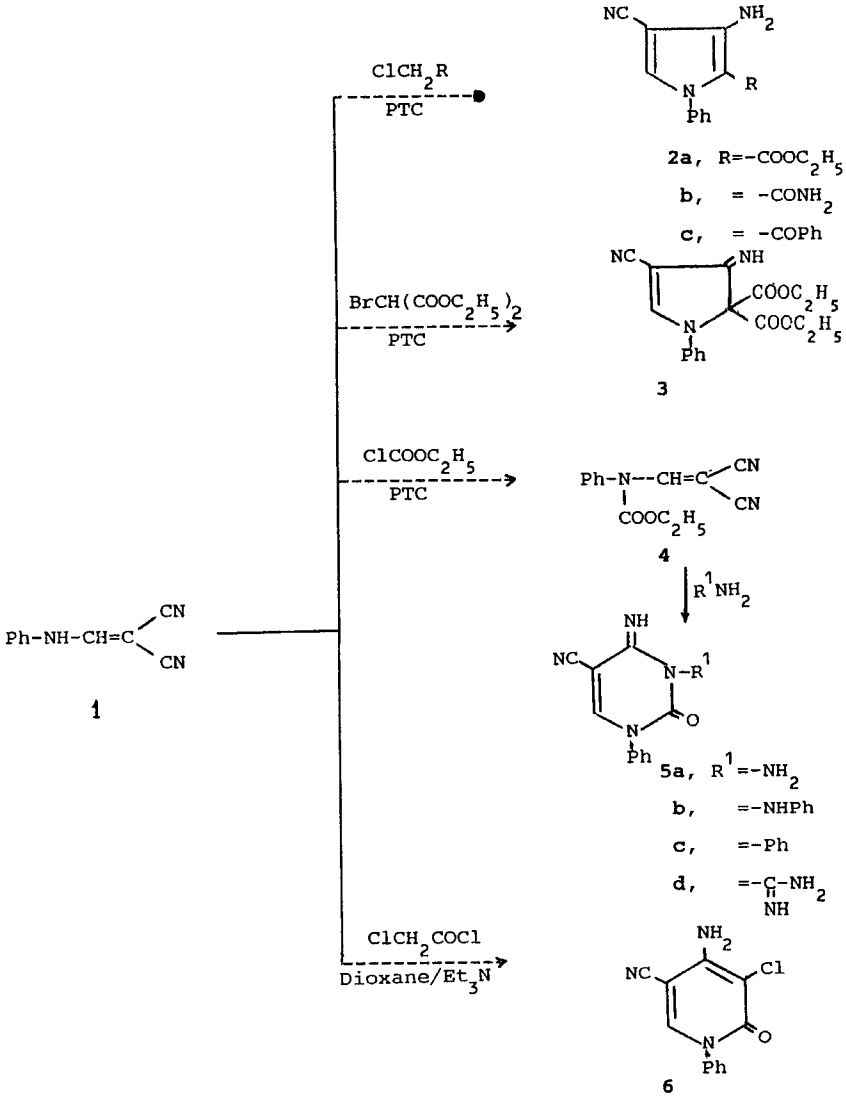
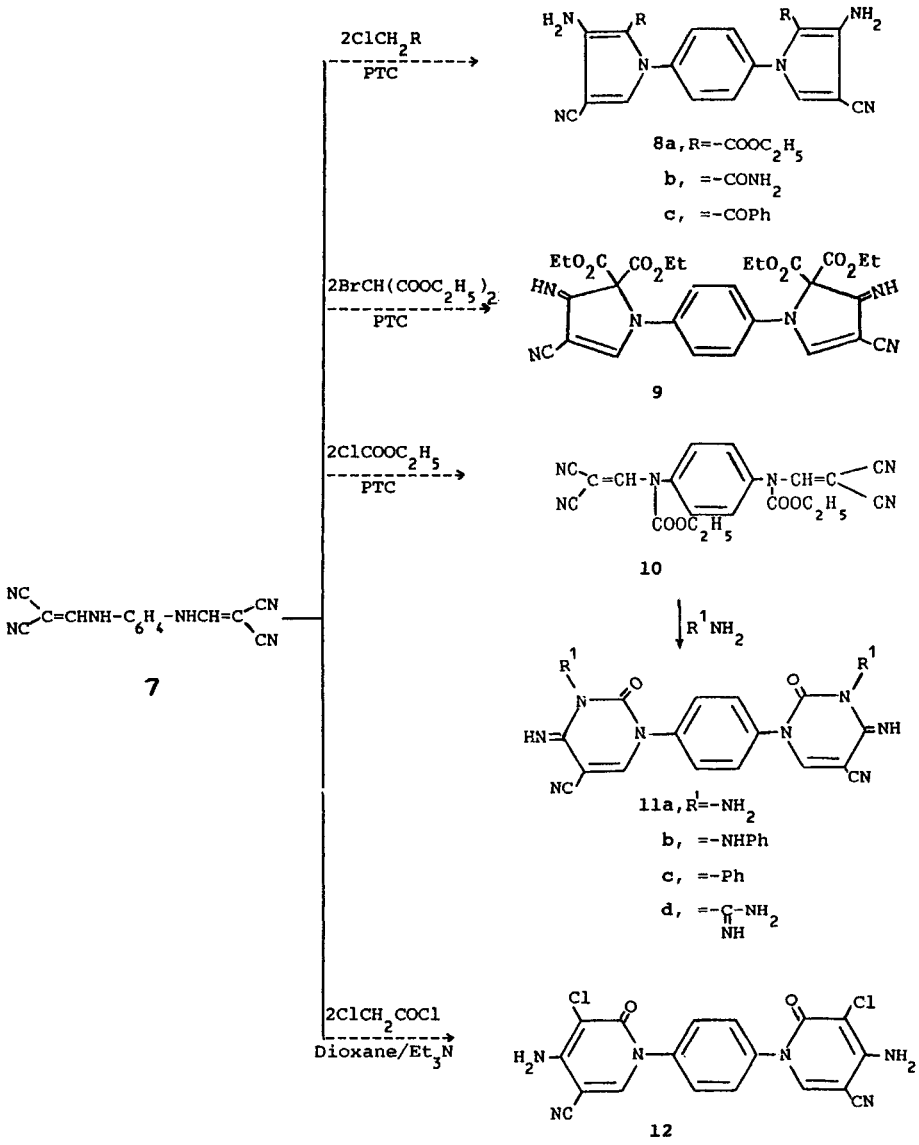


Scheme I



Scheme II

pyrrolylbenzene derivatives 8a-c and 9 (Scheme II). The PTC reactions were performed in solid-liquid two phase systems, organic reactants in dioxan or DMF form the organic phase in which solid K_2CO_3 is suspended. The reaction was catalyzed with TBAB which is unable to transfer carbonate anions (CO_3^{2-}) into the organic phase[8]. The reaction pathway affording the pyrrole derivatives 2,3 and the dipyrrolyl benzene derivatives 8,9 was assumed to proceed via two catalytic cycles. The first one involves a proton abstraction from -NH group in compound 1 on the surface of solid K_2CO_3. The produced anion is transfered along with Q^+ cation as an ion pair A into the organic phase, where it attacks either the methylene or methenyl carbon of the reactive halo compound to give the corresponding N-alkylated product B along with the catalyst molecule Q^+X^-. The second cycle involves the abstraction of H^+ from compound B also at K_2CO_3 surface to give the corresponding anion which transfered into the organic phase along with Q^+ cation. This formed species C undegoes intramolecular cyclization into compound D which affords after protonation the final product along with the catalyst QX which starts a new catalytic cycle, cf. Fig.1. The reaction of compound 1 or 7 with ethyl chloroformate in 1:1 or 1:2 molar ratio using PTC conditions gave the corresponding N-alkylated or N,N-dialkylated products namely, N-ethoxycarbonylanilinomethylene-malononitrile 4 or 1,4-di(N,N-diethoxycarbonylmalononitrilemethyl-eneamino) benzene 10, respectively, cf. Scheme I and II. Compound 4 and 10 were proved to be excellent precursors for the synthesis

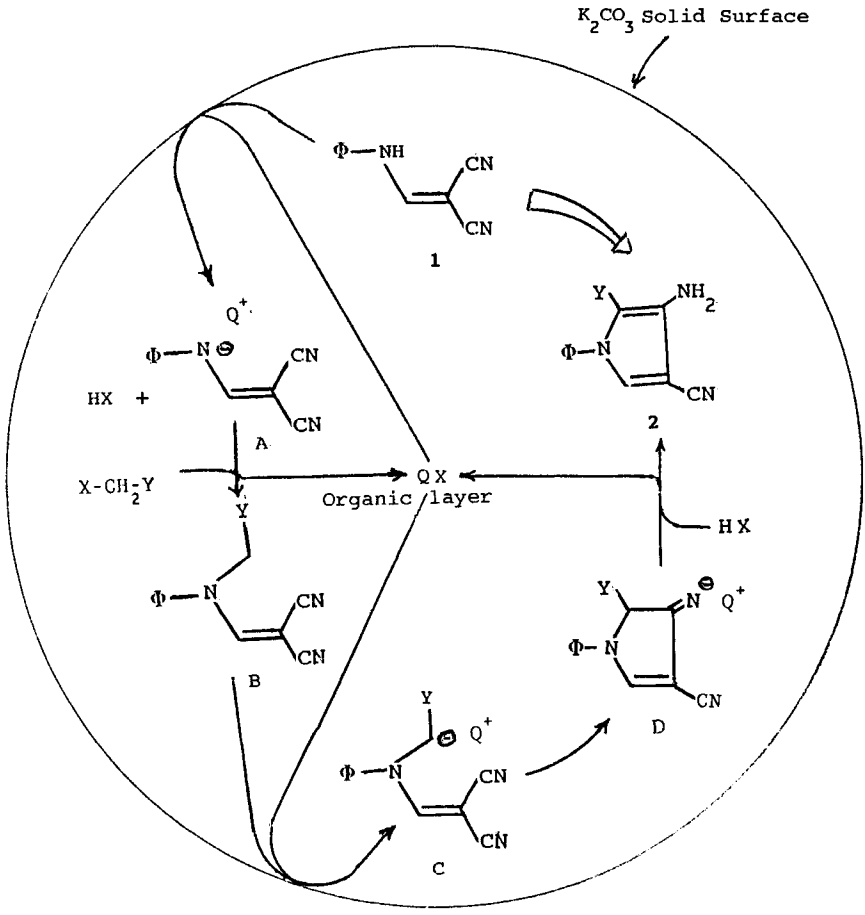


Fig. 1

of pyrimidinone derivatives 5 and 11. Thus, the reaction of 4 or 10 with amino compounds e.g. hydrazine hydrate, phenyl hydrazine, aniline or guanidine hydrochloride in 1:1 or 1:2 molar ratio gave phenylpyrimidin-2-ones 5a-d or the dipyrimidinone derivatives 11a-d, respectively.

The reaction of compound 1 or 7 with chloroacetyl chloride and triethylamine in 1:1:1 or 1:2:2 molar ratio in dry dioxan affords 4-amino-3-chloro-5-cyano-1-phenylpyridin-2-one 6 or 1,4- di(4'-amino-3'-chloro-5'-cyano-2-pyridinon-1'-yl)benzene 12, respectively. The suggested reaction mechanism ivolves a nucleophilic attack of -NH at the carbonyl function with elimination of HCl followed by a nucleophilic attack of the active methylene at the -CN group. The synthetic utilities of the obtained pyridone derivatives is now under investigation.

EXPERIMENTAL

Synthesis of 1,4-di(malononitrilemethyleneamino)benzene 7

A solution of 0.02 mol of ethoxymethylenemalononitrile in 5 mL ethanol was added to 0.01 of *p*-phenylenediamine in 30 mL ethanol. The reaction mixture was stirred for 30 min. at room temperature and the precipitated solid was filtered off, washed with water and recrystallized, cf. Table I.

Synthesis of Substituted Pyrroles 2a-c, 3; Dipyrrolyl benzene derivatives 8a-c, 9; N-ethoxycarbonylanilinomethylenemalononitrile 4 and 1,4-di(N,N-ethoxycarbonylmalononitrilemethyleneamino)benzene 10.

General Procedure

To 3 g of anhydrous potassium carbonate in 40 mL dry dioxan 0.003 mol of compound 1 was added an equimolar amount of the appropriate reactant and the reaction mixture was treated with a

catalytic amount of tetrabutylammonium bromide (TBAB). The reaction of 0.003 mol of compound 7 with 0.006 mol of the same reactants was carried out in K_2CO_3 (3 g)/ DMF (70 mL)/ TBAB system. The reaction mixtures were stirred over different periods of time at the appropriate temperatures, cf. Table I, till the completion of reaction (TLC). The mixtures were filtered, the filterate washed throughly with water, dried over anhydrous $MgSO_4$ and evaporated in vacuo. The residue was washed with water, triturated with pet. ether 40-60 °C to give a solid, which was recrystallized from the appropriate solvent.

Synthesis of 5-cyano-4-imino-1-phenyl-3-substituted pyrimidin-2-ones 5a-d and 1,4-di(5'-cyano-4'-imion-3'-substituted-2'-pyrimidinon-1'-yl)benzene 11a-d.

A mixture of compound 4 (0.003 mol) and the appropriate amino compound (0.0035 mol) in 30 mL ethanol was refluxed for a period between 4-6 h. Compound 10 (0.002 mol) was also reacted with (0.0045 mol) of the appropriate amino compound in 40 mL DMF under reflux for a period between 6-7 h. The reaction mixture was then evaporated in vacuo and the precipitated solid was collected by filteration and recrystallized from the proper solvent to give the titled products 5a-d and 11a-d, respectively, cf. Table I.

Synthesis of 4-amino-3-chloro-5-cyano-1-phenylpyridine-2-one 6 and 1,4-di(4'-amino-3'-chloro-5'-cyano-2'-pyridinon-1'-yl)benzene 12.

To a stirred mixture of compound 1 (0.003 mol) and triethylamine (0.003 mol) in dry dioxan (30 mL), a solution of 0.003 mol

TABLE I

Product	m.p.[a] (Cryst. Solv.)	Reaction time (h) Reaction Temp. °C	Yield %
2a	150-151 (Ethanol)	8/95	85
2b	193 (Ethanol)	4/80	82
2c	225 (Ethanol)	3.5/85	88
3	204-206 (aq.Ethanol)	4/70	70
4	94-95 (aq.Ethanol)	4.5/70	75
5a	155 (Methanol)	6/reflux	85
5b	121 (Methanol)	6/reflux	83
5c*	240 (Ethanol)	4/reflux	65
5d**	>300 (Ethanol)	4/reflux	60
6	147 (Ethanol)	4/35	65
7	>300 (Dioxane/DMF)	0.5/30	95
8a	212-214 (Dioxane)	7.5/80	83
8b	>300 (Dioxane)	8/105	80
8c	255-257 (Ethanol/Dioxane)	7/80	86
9	242-244 (DMF)	6/95	73
10	305 (DMF)	8/32	85
11a	187-188 (Ethanol/Dioxane)	6/reflux	78
11b	>300 (DMF)	7/reflux	76

11c	238-239 (Ethanol)	6/reflux	70
11d**	268-270 (Dioxane/DMF)	7/reflux	68
12	>300 (Dioxane)	5/50	70

*

** The reaction solvent is dioxan.
Equimolar ratio of triethylamine was added to the reaction mixture

Product	Mol. form.[b] Mol. Wt.	Analytical data Calc./Found (%) C	H	N
2a	$C_{14}H_{13}N_3O_2$ (255.28)	65.87 65.64	5.13 5.06	16.46 16.39
2b	$C_{12}H_{10}N_4O$ (226.24)	63.70 63.61	4.45 4.58	24.76 24.87
2c	$C_{18}H_{13}N_3O$ (287.32)	75.25 75.41	4.56 4.73	14.62 14.71
3	$C_{17}H_{17}N_3O_4$ (327.34)	62.38 62.29	5.23 5.34	12.84 12.72
4	$C_{13}H_{11}N_3O_2$ (241.25)	64.72 64.56	4.60 4.47	17.42 17.53
5a	$C_{11}H_9N_5O$ (227.23)	58.14 58.09	3.99 3.71	30.82 30.71
5b	$C_{17}H_{13}N_5O$ (303.32)	67.32 67.45	4.32 4.51	23.09 23.17
5c*	$C_{17}H_{12}N_4O$ (288.35)	70.81 70.64	4.19 4.29	19.43 19.61
5d**	$C_{12}H_{10}N_6O$ (254.25)	56.69 56.52	3.96 3.78	33.05 33.18
6	$C_{12}H_8N_3OCl$ (245.67)	58.67 58.79	3.28 3.11	17.10 17.19
7	$C_{14}H_8N_6$ (260.26)	64.61 64.82	3.10 3.25	32.29 32.18
8a	$C_{22}H_{20}N_6O_4$ (432.45)	49.99 49.72	3.26 3.40	25.91 25.78
8b	$C_{18}H_{14}N_8O_2$ (374.36)	57.75 57.90	3.77 3.56	29.93 29.81

(continued)

TABLE I (continued)

8c	$C_{30}H_{20}N_6O_2$ (496.53)	72.57 72.41	4.06 4.17	16.93 16.82
9	$C_{28}H_{28}N_6O_8$ (576.57)	58.33 58.55	4.89 4.79	14.85 14.69
10	$C_{20}H_{16}N_6O_4$ (404.39)	59.40 59.57	3.99 3.88	20.78 20.63
11a	$C_{16}H_{12}N_{10}O_2$ (376.38)	51.06 51.22	3.21 3.29	37.21 37.34
11b	$C_{28}H_{20}N_{10}O_2$ (528.54)	63.63 63.57	3.81 3.69	26.50 26.65
11c	$C_{28}H_{18}N_8O_2$ (498.51)	67.46 67.32	3.64 3.77	22.48 22.61
11d**	$C_{18}H_{14}N_{12}O_2$ (598.47)	39.13 39.25	2.36 2.27	28.05 28.18
12	$C_{18}H_{10}N_6O_2Cl_2$ (413.22)	52.32 52.53	2.44 2.32	20.34 20.48

Product	IR(Cm^{-1})[c]	^{1}H-NMR[d] (δ ppm)
2a	3448,3335(NH_2), 2215(CN), 1730(CO).	7.70-7.15(m,5H,arom.), 7.05(s,1H, α-pyrrol.), 4.60(s,2H,NH_2), 4.30 -3.90(q,2h,CH_2), 1.20-0.85(t,3H, CH_3).
2b	3292,3210,3110(2NH_2), 2202 (CN), 1680(CO).	7.80-7.20(m,5H,arom), 6.95(s,1H, α-pyrrol), 4.55(s,2H,NH_2), 4.20(s,2h,NH_2).
2c	3436,3323(NH_2), 2210(CN), 1710(CO).	7.80-6.90(m,10H,arom), 7.10(s,1H α-pyrrol), 4.65(s,2h,NH_2).
3	3436,3323(NH), 2213(CN), 1735,1730(2CO).	11.40(s,1H,NH), 7.75-7.15(m,5H,ar -om,), 6.85(s,1H,α-pyrrol), 4.35 -3.95(q,4H,2CH_2), 1.30-0.90(t,6H, 2CH_3).
4	2220,2210(2CN),1755(CO).	8.40(s,1H,CH=), 7.70-7.30(m,5H,ar -om.),4.60-4.15(q,2H,CH_2), 1.65- 1.20(t,3H,CH_3).

5a	3337,3317,3233(NH,NH_2), 2233(CN), 1690(C=O).	11.15(s,1H,NH), 8.55(s,1H,C_6-H Pyrimidinone), 7.85-6.85(m,10H, arom.),4.90(s,2H,NH_2).
5b	3317,3250(2NH), 2213(CN) 1680(C=O).	11.30(s,1H,NH), 11.15(s,1H,NH), 8.15(s,1H,C_6-H Pyrimidinone), 7.75-7.20(m,5H,arom.).
5c	3214(NH), 2213(CN), 1685 (C=O).	11.15(s,1H,NH), 8.20(s,1H,C_6-H Pyrimidinone), 7.90-7.10(m,10H, arom.).
5d	3427,3337,3314,3270(2NH, NH_2), 2200(CN), 1685(C=O)	11.60(s,1H,NH), 11.20(s,1H,NH), 8.25(s,1H,C_6-H Pyrimidinone), 7.75-7.15(m,5H,arom.), 4.15(s, 2H,NH_2).
6	3460,3355(NH_2), 2220(CN), 1690(C=O).	8.10(s,1H,C_6-H Pyrimidinone), 7.80-7.15(m,5H,arom.), 4.85(s, 2H,NH_2).
7	3354,3340(2NH), 2215,2200 (4CN).	11.15(s,2H,2NH), 8.45(s,2H,2CH=), 7.75-7.30(m,4H,arom.).
8a	3456,3350,3214($2NH_2$), 2225 2215(2CN), 1735,1725(2C=O)	7.75-7.25(m,4H,arom.), 7.10(s,2H, α-,α'-pyrrole), 5.95(br,4H,$2NH_2$), 4.35-3.80(m,4H,$2CH_2$), 1.55-0.95 (m,6H,$2CH_3$).
8b	3466,3392,3221,3143($4NH_2$) 2220,2200(2CN), 1690,1685 (2C=O).	7.80-7.25(m,4H,arom.), 7.05(s,2H, α-,α'-Pyrrole), 5.85(br,4H,$2NH_2$), 4.15(br,4H,$2NH_2$).
8c	3427,3298,3221($2NH_2$), 2213,2200(2CN), 1715,1710 (2C=O).	7.90-7.15(m,4H,arom.), 7.10(s,2H, α-,α'-Pyrrole), 5.75(br,4H,$2NH_2$).
9	3298,3280(2NH), 2230,2225 (2CN), 1740,1735(4C=O)	11.30(br,2H,2NH), 7.70-7.15(m,4H, arom.), 7.05(s,2H,α-,α'-Pyrrole), 4.55-3.85(m,8H,$4CH_2$), 1.55-0.80 (m,12H,$4CH_3$).
10	2225,2220(4CN), 1735,1730 (2C=O)	7.75-7.20(m,4H,arom.), 4.50-3.85 (m,4H,$2CH_2$), 1.45-0.85(m,6H,$2CH_3$)

(continued)

TABLE I (continued)

11a	3443,3430,3385,3316(2NH, $2NH_2$), 2216,2200(2CN), 1695,1690(2C=O)	11.45(br,2H,2NH), 8.25(s,2H,C_6-H Pyrimidinone), 7.70-7.15(m,4H, arom.), 6.20(br,4H,$2NH_2$)
11b	3445,3410,3338,3218(4NH) 2230,2220(2CN), 1690,1685 (2C=O)	11.55(br,2H,2NH), 10.85(br,2H, 2NH), 8.25(s,2H,C_6-H Pyrimidinone), 7.80-7.15(m,14H,arom.),
11c	3324,3295(2NH), 2212,2199 (2CN), 1696,1690(2C=O)	11.30(br,2H,2NH), 8.25(s,2H,C_6-H Pyrimidinone), 7.85-7.15(m,14H, arom.).
11d	3445,3410,3330,3315,3285 (4NH,$2NH_2$), 2220,2205(2CN) 1690,1685(2C=O)	11.25(br,2H,2NH), 10.65(br,2H, 2NH), 8.35(s,2H,C_6-H Pyrimidinone , 7.70-7.15(m,4H,arom.), 3.15(br, 4H,$2NH_2$)
12	3350,3292,3208($2NH_2$), 2225,2220(2CN), 1690,1685 (2C=O)	8.15(s,2H,6,6'-Pyridinone), 7.80 -7.25(m,4H,arom.), 6.15(br,4H, $2NH_2$) .

[a]) Uncorrected [b])Satisfactory microanalyses obtained C; ± 0.35% H;± 0.40% N; ± 0.20%, [c])Measured by Nicolet FT-IR 71(Spectrophotometer [d])Measured by a Varian EM 360 L Spectrometer at 60 MHz using TMS as internal Standard.

of chloroacetyl chloride in 30 mL of dry dioxan was added dropwise. Compound 7 (0.002 mol) along with triethylamine (0.004 mol) in 30 mL DMF was also treated, under stirring, with 0.004 mol chloroacetyl chloride in 5 mL dry DMF. The two reaction mixtures were stirred for 4 h. at 35 °C or for 5 h. at 50 °C, respectively. After completion of the reaction (PTC), the reaction mixture was filtered off, evaporated in vacuo and the residue was washed with water, triturated with pet. ether 40-60°C to afford a solid, which was recrystallized from the proper solvent, cf. Table I.

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