2-HALOALKYLIDENEPROPANEDINITRILES IN THE SYNTHESIS OF FUSED PYRIMIDINES

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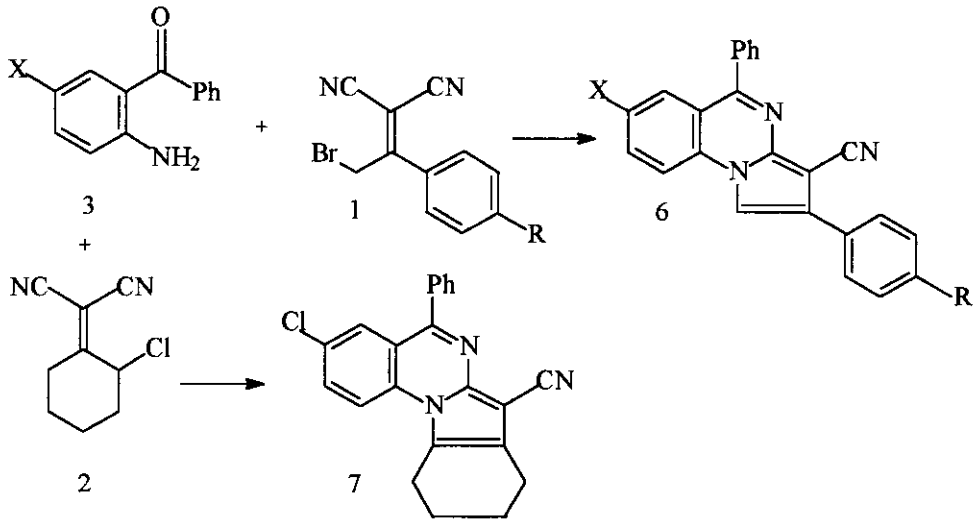
Abstract - A single step synthesis of various heterocycles such as 2-cyano-5-phenylpyrrolo[1,2-*a*]quinazolines (6), 5-phenyl-7-cyano-8,9,10,11-tetrahydroindolo[1,2-*a*]quinazoline (7), 2-cyanocyclopenta[4,5]thieno[3,2-*e*]pyrrolo[1,2-*a*]-pyrimidin-5(4*H*)-ones (9) and 4-(2-amino-3-cyanopyrrol-1-yl)-5-carbethoxythiazole-2-thiones (10) have been reported using 2-haloalkylidenepropanedinitriles (1) and (2) with 5-substituted 2-aminobenzophenones (3), 2-amino-3-carbethoxycyclopenta[4,5]thiophenes (4) and 3-substituted 4-amino-5-carbethoxythiazole-2-thiones (5) respectively.

o-Aminonitriles, the readily accessible building blocks for the construction of many important heterocycles, have been prepared using 2-haloalkylidenepropanedinitriles under Gewald conditions.[1-3] Moreover, a variety of heterocyclic ring systems including pyrroloimidazole,[4] thiazole,[5] thiazepine,[6] pyrroloquinazoline,[7-9] and pyrrolothienopyrimidines[9,10] have been reported using 2-haloalkylidenepropanedinitriles. Herein, we wish to report the synthesis of 1,7-disubstituted 2-cyano-5-phenylpyrrolo[1,2-*a*]quinazolines (6), 3-chloro-5-phenyl-7-cyano-8,9,10,11-tetrahydroindolo[1,2-*a*]quinazoline (7), 1-substituted 2-cyanocyclopenta[4,5]-thieno[3,2-*e*]pyrrolo[1,2-*a*]pyrimidin-5(4*H*)-ones (9), and 3-substituted 4-(1-substituted 2-amino-3-cyanopyrrol-1-yl)-5-carbethoxythiazole-2-thiones (10) in order to establish the utility and versatility of 2-haloalkylidenepropanedinitriles (1) and (2).

Treatment of 5-substituted 2-aminobenzophenones (3) with 2-bromoalkylidenepropanedinitriles (1) in propanol at 65-70^{0}C afforded 1,7-disubstituted 2-cyano-5-phenylpyrrolo[1,2-*a*]quinazolines (6). Analogous treatment of 3 with 2-chlorocyclohexalidenepropanedinitrile (2) yielded 3-chloro-5-phenyl-7-cyano-8,9,10,11-tetrahydroindolo[1,2-*a*]quinazoline (7) (Scheme 1).

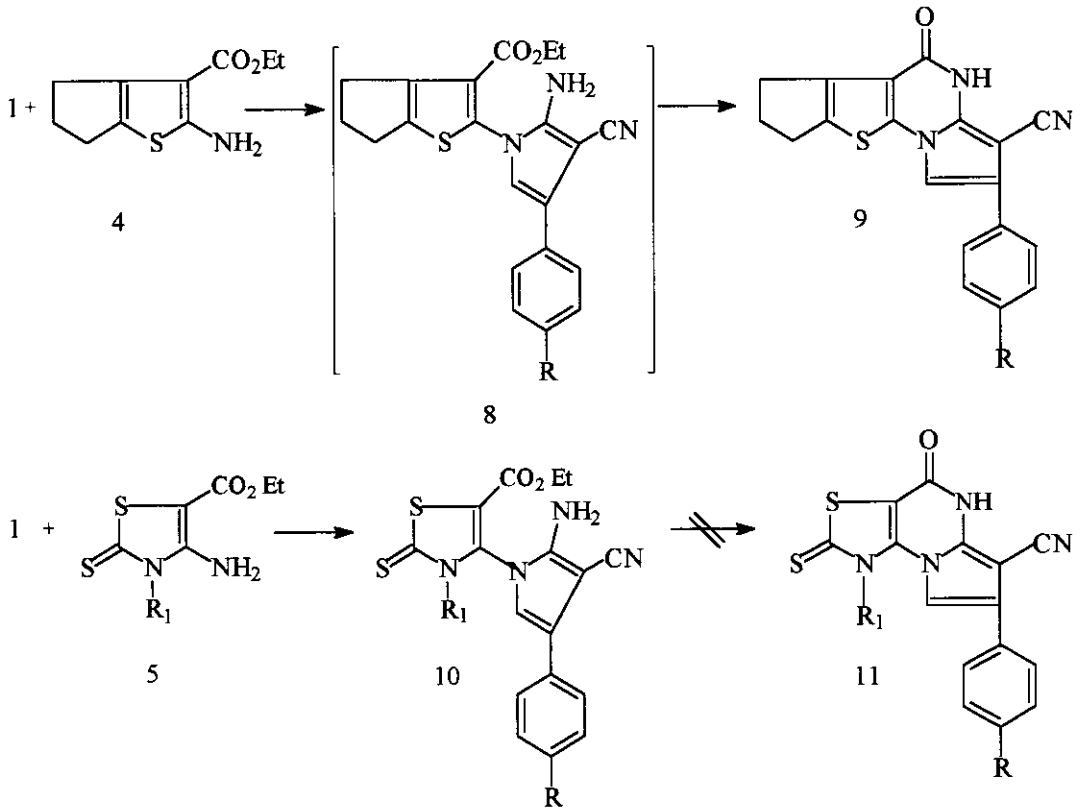


Scheme 1

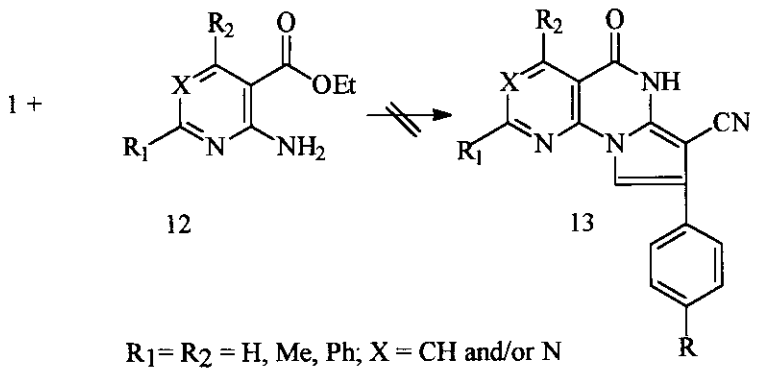
UV(methylene chloride) spectra of compounds (6) and (7) exhibited two prominent λmax in the region 246-393 nm. A sharp characteristic band for C≡N near 2200 cm^{-1} was found in IR(KBr) spectra of compounds (6) and (7) along with the absorptions in the region 1596-1484 cm^{-1} (C=C, C=N). The absence of absorptions due to amino and carbonyl groups near 3400-3200 and 1700 cm^{-1} respectively proved the formation of tricyclic products (6) and (7). ^1H NMR(DMSO-d_6) of 6 exhibited a multiplet near δ 6.90-7.80 due to aromatic protons. Aromatic protons(9H) of 7 were resonated at δ 6.90-7.70, while methylene protons (8H) were observed at δ 3.13-3.50 in the form of multiplet.

Further, in order to establish the versatility of 2-bromoalkylidenepropanedinitriles (1) as synthons, 1 reacted with 2-amino-3-carbethoxycyclopenta[4,5]thiophenes (4) and 3-substituted 4-amino-5-carbethoxythiazole-2-thiones (5). When 1 reacted with 4 in propanol at 70-80 ^0C the intermediates (8) formed were easily underwent cyclization forming triheterocycles (9) in a single step and in no case intermediates (8) were isolated. Compounds (1) on reaction with 5 also predicted to proceed in the similar way to provide thiazolopyrrolopyrimidones (11), but instead in all the attempted reactions the uncyclic products 3-substituted 4-(1-substituted 2-amino-3-cyanopyrrol-1-yl)-5-carbethoxythiazole-2-thiones (10) were recovered (Scheme 2).

The reactions between 1 and π-deficient systems having pyridine or pyrimidine nucleus (12) were unsuccessful under the conditions exploited for π-excessive substrates (3) and (4) and in all the cases starting compounds (12) were recovered (Scheme 3). Therefore, it could easily be concluded that the formation of triheterocycles is facilitated with a π-excessive ring such as benzene, thiophene etc., while it is hindered in π-deficient rings such as pyridine and pyrimidine.



Scheme 2



$R_1 = R_2 = H$, Me, Ph; X = CH and/or N

Scheme 3

IR(KBr) spectra of 9 showed absorptions near 3120 and 3050-2840 cm^{-1} for N-H and C-H along with the characteristic C=C, C=N stretching vibrations at 1604-1492 cm^{-1}. The sharp bands near 2210 and 1670 cm^{-1} were assigned to cyano and carbonyl functionalities respectively. ^1H NMR(DMSO-d_6) of 9 exhibited multiple bands due to methylene protons(6H) in the region δ 3.15-3.70, while a multiplet due to aromatic protons was obtained at δ 6.85-8.45. The NH ring proton was absorbed downfield at δ 10.30-10.50.

IR(KBr) spectra of 10 exhibited two prominent bands in the region 3450-3280 cm^{-1} for amino group which supported the formation of uncyclic products (10). A sharp absorption for cyano group was obtained near 2210 cm^{-1} together with a sharp absorption for carbonyl moiety of ester group near 1670 cm^{-1}. The signals due to C=C, C=N and C=S stretching vibrations were obtained near 1596-1488 and1300-1200 cm^{-1} respectively. Moreover the presence of triplet of CH_3(3H) at δ 1.20-1.40 and quartet of CH_2(2H) at δ 4.10-4.40 respectively due to ethyl protons togather with a broad absorption due to amino protons(2H) near δ 5.50-5.60. Aromatic protons were resonated at δ 7.10-7.80 in the form of multiplet.

EXPERIMENTAL

Melting points were determined on electrothermal apparatus(capillary method) and are uncorrected. The IR spectra were performed on a Buck scientific spectrophotometer using potassium bromide technique. The TLC were performed using silica gel G and spots were exposed in iodine vapour. The ^{1}H NMR spectra were taken in DMSO-d_6 on Varian model 100-400 spectrometer using TMS as an internal standard. MS spectra were recorded on Jeol D-300 Mass Spectrometer.

The procedures given for the synthesis of 6,7,9 and 10 were utilized in the formation of compounds (6a-6h, 7, 9a-9d and 10a-10c).

1,7-Disubstituted 2-cyano-5-phenylpyrrolo[1,2-*a*]quinazolines (6a-6h) (General procedure)

To the well stirred solution of 2-bromo-1-arylalkylidenepropanedinitriles[1] (2) (0.011 mol) in propanol(40 mL) was added the solution of 5-substituted 2-aminobenzophenones (3) (0.01 mol) in propanol(20 mL) in portions at 65 ^{0}C during the period of 30 min. After the addition was completed the reaction mixture was further stirred for 5-6 h at the same temperature and for 2 h at rt. The cold reaction mixture was poured on to the crushed ice(150 g), the solid separated was filtered, washed with aqueous ethanol(20 % v/v) followed by water, dried and crystallized from a mixture of ethanol : DMF(4 : 6) to yield the following pyrrolo[1,2-*a*]quinazolines (6).

1,5-Diphenyl-2-cyanopyrrolo[1,2-*a*]quinazoline (6a). yield : 41 %; mp : 287-289 ^{0}C; UV(methylene chloride) : 375(4.18), 283(4.51); IR(KBr) : 2220(CN) cm^{-1}; ^{1}H NMR(DMSO-d_6) : δ 6.90-7.80 (m, 15H, Ar-H); MS : 345(M^+). Anal. Calcd for $C_{24}H_{15}N_3$: C, 83.45; H, 4.38; N, 12.17. Found : C, 83.78; H, 4.59; N, 12.37.

1-(4-Methylphenyl)-2-cyano-5-phenylpyrrolo[1,2-*a*]quinazoline (6b). yield : 41 %; mp : 281-283 ^{0}C; UV(methylene chloride) : 373(4.22), 283(4.43); IR(KBr) : 2210(CN) cm^{-1}; ^{1}H NMR(DMSO-d_6) : δ 2.45(s, 3H, CH_3), 7.10-8.00 (m, 14H, Ar-H); MS : 359(M^+). Anal. Calcd for $C_{25}H_{17}N_3$: C, 83.54; H, 4.77; N, 11.69. Found : C, 83.78; H, 4.54; N, 11.89.

1-(4-Methoxyphenyl)-2-cyano-5-phenylpyrrolo[1,2-*a*]quinazoline (6c). yield : 40 %; mp : 247-249 ^{0}C; UV(methylene chloride) : 374(4.18), 280(4.49); IR(KBr) : 2210(CN) cm^{-1}; ^{1}H NMR(DMSO-d_6) : δ 3.17(s, 3H, OCH_3), 7.25-8.17(m, 14H, Ar-H); MS : 375(M^+). Anal. Calcd for $C_{25}H_{17}N_3O$: C, 79.78; H, 4.57; N, 11.19. Found : C, 78.59; H, 4.48; N, 11.32.

1-(4-Chlorophenyl)-2-cyano-5-phenylpyrrolo[1,2-*a*]quinazoline (6d). yield : 48 %; mp : 277-279 ^{0}C; UV(methylene chloride) : 282(4.47), 247(4.49); IR(KBr) : 2220(CN) cm^{-1}; ^{1}H NMR(DMSO -d_6) : δ 7.20-8.10 (m, 14H, Ar-H); MS : 382(M+2). Anal. Calcd for $C_{24}H_{14}N_3Cl$: C, 75.84; H, 3.71; N, 11.06. Found : C, 75.58; H, 3.61; N, 11.36.

1,5-Diphenyl-2-cyano-7-chloropyrrolo[1,2-*a*]quinazoline (6e). yield : 43 %; mp : 308-310 ^{0}C; UV(methylene chloride) : 282(4.47), 247(4.49); IR(KBr) : 2220(CN) cm^{-1}; ^{1}H NMR(DMSO-d_6) : δ 7.00-8.10 (m, 14H, Ar-H); MS : 382(M+2). Anal. Calcd for $C_{24}H_{14}N_3Cl$: C, 75.84; H, 3.71; N, 11.06. Found : C, 75.58; H, 3.61; N, 11.36.

1-(4-Methylphenyl)-2-cyano-5-phenyl-7-chloropyrrolo[1,2-*a*]quinazoline (6f). yield : 42 %; mp : 285-287 ^{0}C; UV(methylene chloride) : 292(4.47), 246(4.45); IR(KBr) : 2210(CN) cm^{-1}; ^{1}H NMR(DMSO-d_6) : δ 2.55(s, 3H, CH_3); 7.00-8.10 (m, 13H, Ar-H); MS : 396(M+2). Anal. Calcd for $C_{25}H_{16}N_3Cl$: C, 76.23; H, 4.10; N, 10.67. Found : C, 76.03; H, 4.39; N, 10.41.

1-(4-Methoxyphenyl)-2-cyano-5-phenyl-7-chloropyrrolo[1,2-*a*]quinazoline (6g). yield : 40 %; mp : 302-304 ^{0}C; UV(methylene chloride) : 273(4.15), 268(4.16); IR(KBr) : 2210(CN) cm^{-1}; ^{1}H NMR(DMSO-d_6) : δ 3.85(s, 3H, OCH_3); 7.00-8.10 (m, 13H, Ar-H); MS : 412(M+2). Anal. Calcd for $C_{25}H_{16}N_3OCl$: C, 73.26; H, 3.94; N, 10.25. Found : C, 73.54; H, 4.21; N, 10.59.

1-(4-Chlorophenyl)-2-cyano-5-phenyl-7-chloropyrrolo[1,2-*a*]quinazoline (6h). yield : 51 %; mp : 321-323 ^{0}C; UV(methylene chloride) : 283(4.51), 253(4.52); IR(KBr) : 2210(CN) cm^{-1}; ^{1}H NMR(DMSO-d_6) : δ 3.85(s, 3H, OCH_3); 7.10-8.10 (m, 13H, Ar-H); MS : 416(M+2). Anal.Calcd for $C_{24}H_{13}N_3Cl_2$: C, 69.58; H, 3.17; N, 10.14. Found : C, 69.76; H, 3.39; N, 10.01.

3-Chloro-5-phenyl-7-cyano-8,9,10,11-tetrahydroindolo[1,2-*a*]quinazoline (7).

To the well stirred solution of 2-chlorohexalidenepropanedinitriles[1] (2) (1.853 g, 0.011 mol) in propanol(40 mL) was added the solution of 2-amino-5-chlorobenzophenone (3) (2.315 g, 0.01 mol) in propanol(20 mL) in portions at 65 ^{0}C over a period of 30 min. After the addition was completed, the reaction mixture was further stirred for 6 h at the same temperature and for 2 h at rt. The cold reaction mixture was poured on to the crushed ice(150 g), the solid separated was filtered, washed with aqueous ethanol(20 % v/v) followed by water, dried and crystallized from a mixture of ethanol : DMF(6:3) to obtain 40 % yield of 7. mp : 310-312 ^{0}C; UV(methylene chloride) : 394(3.98), 246(4.48); IR(KBr) : 3080-2850(CH),

2220(CN) cm^{-1}; ^1H NMR(DMSO-d_6) : δ 3.15-3.50(m, 8H, $(CH_2)_4$); 6.90-7.70 (m, 12H, Ar-H); MS : 360(M+2). Anal. Calcd for $C_{22}H_{16}N_3Cl$: C, 73.84; H, 4.51; N, 11.74. Found : C, 73.61; H, 4.81; N, 11.99.

1-Substituted 2-cyanocyclopenta[4,5]thienopyrrolo[1,2-*a*]pyrimidin-5(4*H*)-ones (9) (General procedure) The solution of 2-bromo-1-arylalkylidenepropanedinitriles (1) (0.01 mol) in propanol(40 mL) was added the solution of 2-amino-3-carbethoxycyclopenta[4,5]thiophenes[11] (4) in propanol(20 mL) at 65-70 ^{0}C. After the addition was complited the reaction mixture was stirred at 70-80 ^{0}C temperature for 6-7 h and for 1 h at rt. The cold reaction mixture was poured on to the crushed ice, solid obtained was filtered, washed with aqueous ethanol(20 % v/v) followed by water, dried and crystallized from DMF:ethanol(6 : 4) mixture.

1-Phenyl-2-cyanocyclopenta[4,5]thienopyrrolo[1,2-*a*]pyrimidin-5(4*H*)-one (9a). yield : 40%; mp : 285-287 ^{0}C; IR(KBr) : 3120(NH), 2990-2850(CH), 2210(CN), 1676(CO) cm^{-1}; ^1H NMR(DMSO-d_6) : δ 3.15-3.70(m, 6H, $(CH_2)_3$); 6.85-8.10 (m, 12H, Ar-H); 10.50 (s, 1H, NH); MS : 331(M^+). Anal. Calcd for $C_{19}H_{13}N_3OS$: C, 68.86; H, 3.93; N, 12.68. Found : C, 69.02; H, 4.20; N, 12.89.

1-(4-Methylphenyl)-2-cyanocyclopenta[4,5]thienopyrrolo[1,2-*a*]pyrimidin-5(4*H*)-one (9b). yield : 40%; mp : >360 ^{0}C; IR(KBr) : 3124(NH), 3010-2860(CH), 2220(CN), 1670(CO) cm^{-1}; ^1H NMR(DMSO-d_6) : δ 2.60(s, 3H, CH_3); 3.15-3.70 (m, 6H, $(CH_2)_3$); 7.15-8.40 (m, 12H, Ar-H); 10.30 (s ,1H, NH); MS : 345(M^+). Anal. Calcd for $C_{20}H_{15}N_3OS$: C, 69.54; H, 4.27; N, 12.16. Found : C, 69.90; H, 4.45; N, 11.96.

1-(4-Methoxyphenyl)-2-cyanocyclopenta[4,5]thienopyrrolo[1,2-*a*]pyrimidin-5(4*H*)-one (9c). yield : 45%; mp : 336-338 ^{0}C; IR(KBr) : 3120(NH), 3010-2860(CH), 2210(CN), 1672(CO) cm^{-1}; ^1H NMR(DMSO-d_6) : δ 3.20-3.65 (m, 6H, $(CH_2)_3$); 3.90 (s, 3H, OCH_3); 7.20-8.45(m, 12H, Ar-H); 10.30 (s ,1H, NH); MS : 361(M^+). Anal. Calcd for $C_{20}H_{15}N_3O_2S$: C, 66.46; H, 4.18; N, 11.62. Found : C, 66.66; H, 4.29; N, 11.51.

1-(4-Chlorophenyl)-2-cyanocyclopenta[4,5]thienopyrrolo[1,2-*a*]pyrimidin-5(4*H*)-one (9d). yield : 48%; mp : 313-315 ^{0}C; IR(KBr) : 3128(NH), 2990-2850(CH), 2210(CN), 1672(CO) cm^{-1}; ^1H NMR(DMSO-d_6) : δ 3.15-3.70(m, 6H, $(CH_2)_3$); 6.90-7.70 (m, 12H, Ar-H); 10.60 (s, 1H, NH); MS : 368(M+2). Anal. Calcd for $C_{19}H_{12}N_3OClS$: C, 62.38; H, 3.31; N, 11.49. Found : C, 62.58; H, 3.73; N, 11.71.

3-Substituted 4-(2-amino-3-cyano-4-substituted pyrrol-1-yl)-5-carbethoxythiazole-2-thiones (10) (General procedure) To the well stirred solution of 2-bromo-1-arylalkylidenepropanedinitriles (1) (0.01 mol) in DMF (50 mL) heated at 65 ^{0}C was added powdered 3-substituted 4-amino-5-carbethoxythiazole-2-thiones[12] (5) (0.01 mol) portionwise and the reaction mixture was stirred at 75-80 ^{0}C for 6-8 h and for 1 h at rt. The solution obtained was added to crushed ice(150 g), solid separated was filtered, washed with water followed by ethanol(20 % v/v), dried and crystallized from a mixture of DMF : ethanol (4:6).

3-Phenyl-4-(2-amino-3-cyano-4-phenylpyrrol-1-yl)-5-carbethoxythiazole-2-thione (10a). yield : 40%; mp : 295-297 ^{0}C; IR(KBr) : 3430, 3320(NH), 2220(CN), 1670(CO),1290, 1200(CS) cm^{-1}; ^{1}H NMR(DMSO-d_6) : δ 1.20-1.40 (t, J = 6.2 Hz, 3H, CH_2CH_3); 4.10-4.30(q, J = 6.2 Hz, 2H, CH_2CH_3); 5.50-5.60 (s, 2H, NH_2); 7.30-7.80 (m, 13H, Ar-H); MS : 446(M^+). Anal. Calcd for $C_{23}H_{18}N_4O_2S_2$: C, 61.86; H, 4.06; N, 12.55. Found : C, 61.49; H, 4.16; N, 12.69.

3-Phenyl-4-[2-amino-3-cyano-4-(methoxyphenyl)pyrrol-1-yl]-5-carbethoxythiazole-2-thione (10b). yield : 33%; mp : 269-271 ^{0}C; IR(KBr) : 3420, 3290(NH), 2220(CN), 1680(CO),1300, 1200(CS) cm^{-1}; ^{1}H NMR(DMSO-d_6) : δ 1.20-1.35(t, J = 6.0 Hz, 3H, CH_2CH_3); 3.90-4.00 (s, 3H, OCH_3); 4.20-4.40 (q, J = 6.0 Hz, 2H, CH_2CH_3); 5.50-5.60 (s, 2H, NH_2); 7.10-7.70 (m, 12H, Ar-H); MS : 476(M^+). Anal. Calcd for $C_{24}H_{20}N_4O_3S_2$: C, 60.48; H, 4.23; N, 11.76. Found : C, 60.21; H, 4.01; N, 11.39.

3-(4-Chlorophenyl)-4-(2-amino-3-cyano-4-phenylpyrrol-1-yl)-5-carbethoxythiazole-2-thione (10c). yield : 40%; mp : 268-270 ^{0}C; IR(KBr) : 3400, 3280(NH), 2205(CN), 1670(CO), 1300, 1210(CS) cm^{-1}; ^{1}H NMR(DMSO-d_6) : δ 1.20-1.40 (t, J = 6.3 Hz, 3H, CH_2CH_3); 4.10-4.30(q, J = 6.3 Hz, 2H, CH_2CH_3); 5.50-5.55(s, 2H, NH_2); 7.30-7.85(m, 12H, Ar-H); MS : 483(M+2). Anal. Calcd for $C_{23}H_{17}N_4O_2ClS_2$: C, 57.43; H, 3.56; N, 11.65. Found : C, 57.05; H, 3.81; N, 11.44.

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