

The synthesis of potential DNA intercalaters. 1. Heterocycles from the reaction of aryl bis-isothiocyanates

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Abstract

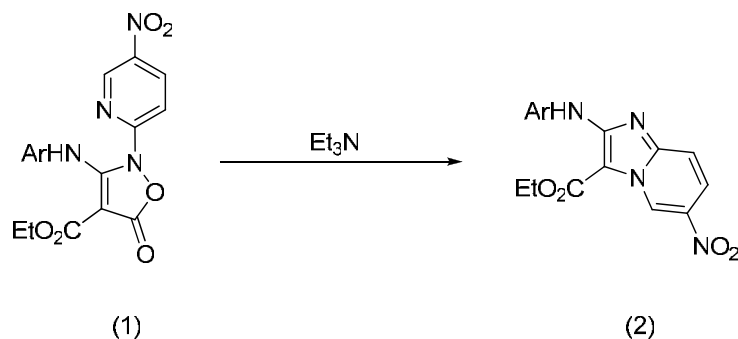
1,3-Bis(isoxazol-3-ylamino)benzenes, substituted on isoxazole-nitrogen with a pyrimidine group, react with triethylamine in ethanol under reflux to afford the corresponding 2-indolylaminoimidazopyrimidine derivatives.

Keyword: Aryl bis-isothiocyanates, 1,3-bis(isoxazol-3-ylamino)benzenes, 2-chloropyrimidine, base induced rearrangement, indolylaminoimidazopyrimidine

Introduction

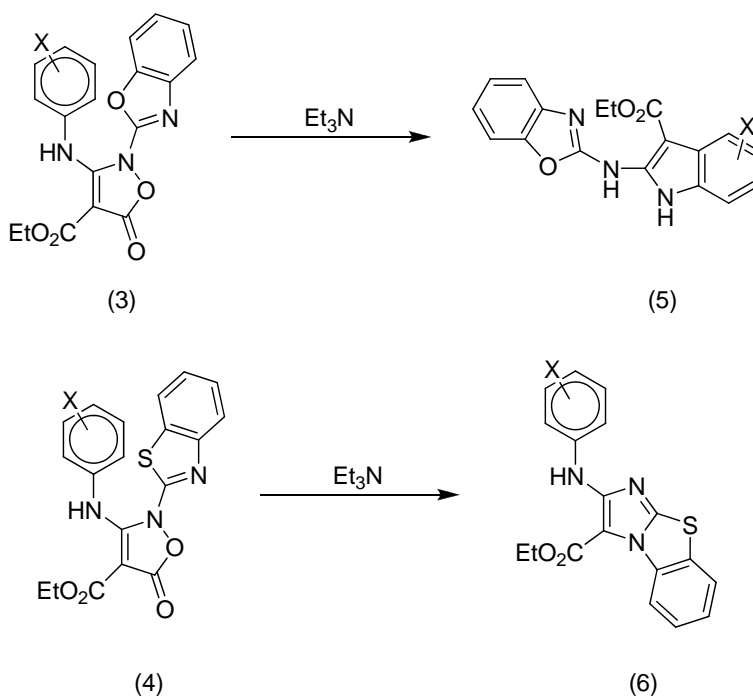
Prager and co-workers have reported¹ that 2-aryl-3-arylaminoisoxazol-5(2H)-ones undergo solvolysis in the presence of potassium carbonate to form either imidazopyridines or indoles, and have suggested the reaction proceeds via the formation of 1,3-dipoles that undergo intramolecular cyclisation.

We have also reported² that arylaminoisoxazol-5(2H)-ones, substituted on nitrogen with a nitropyridine group (**1**), react with triethylamine in ethanol under reflux condition to provide a convenient synthesis of ethyl 2-arylaminoimidazo[1,2-a]pyridine-3-carboxylates (**2**) (Scheme 1).



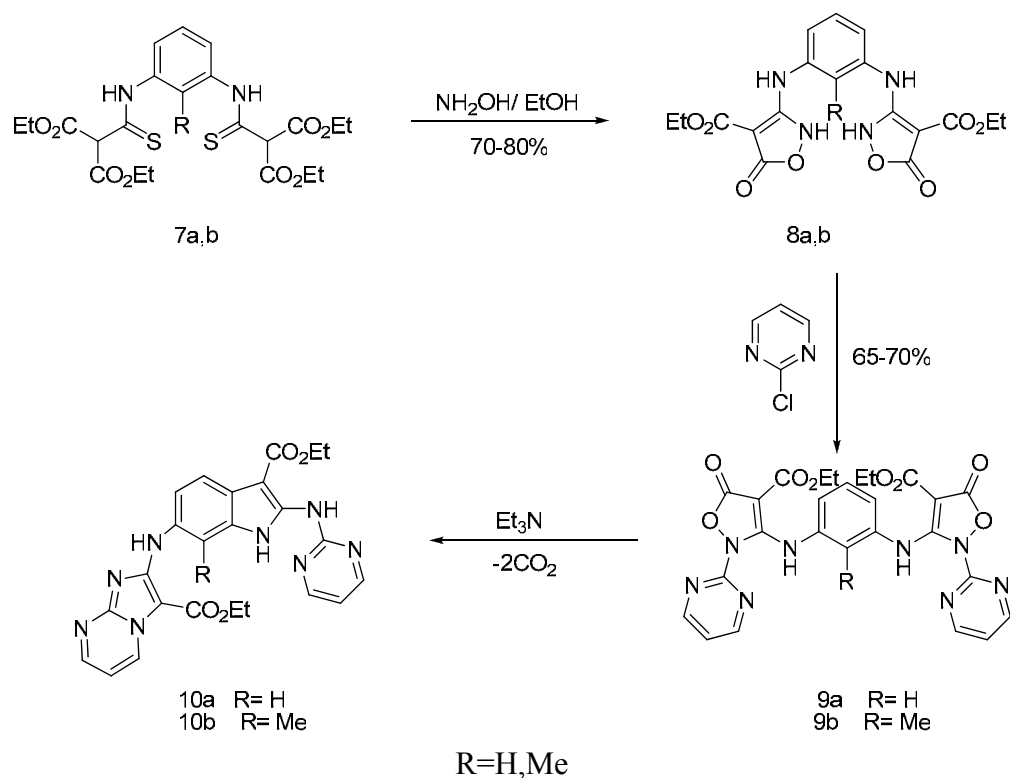
Scheme 1

We have recently extended this work by noting^{3,4} that the reaction of 3-(4-substituted-phenyl)aminoisoxazol-5(2H)-ones (**3**) and (**4**) with triethylamine leads to the formation of indoles (**5**), or imidazobenzothiazoles (**6**) respectively, and carbon dioxide, an outcome that is formally the same as that achieved by photolysis or pyrolysis⁵ (Scheme 2).



Scheme 2

In this paper we report the synthesis of new 1,3-bis(isoxazol-3-ylamino)benzenes and their isoxazolyl-N-substituted derivatives, and the rearrangement of the latter in the presence of triethylamine in ethanol under reflux to produce the indolylaminoimidazopyrimidine derivatives (Scheme 3). The reaction is formally a hybrid of the two reaction pathways noted previously, and provides suitable synthetic intermediates for a series of new heterocycles that could be expected to have pharmaceutical applications.^{6,7}



Scheme 3

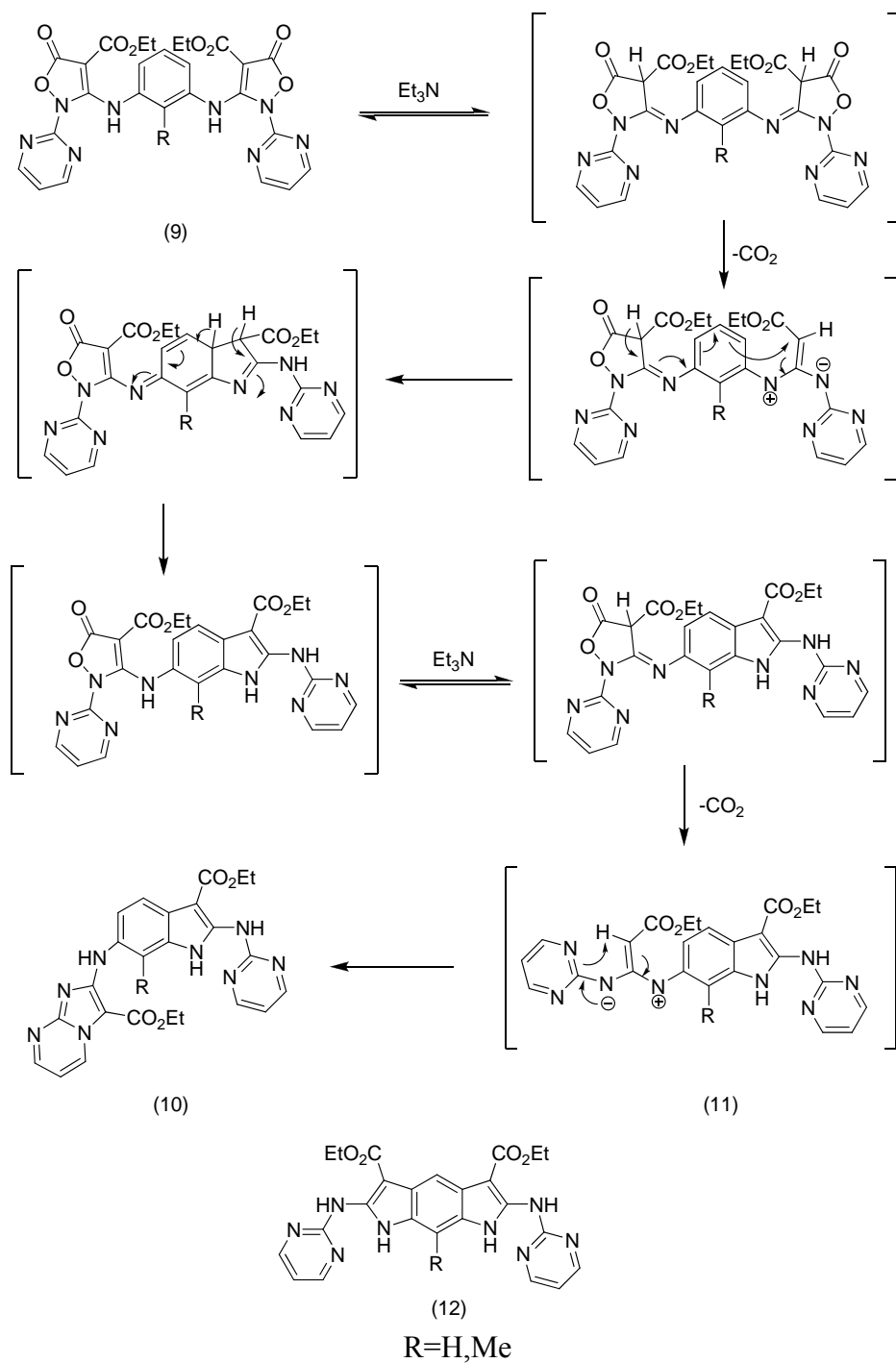
Results and Discussion

The isoxazolones **8a,b** were prepared by reaction of the corresponding thiocarbamates **7a,b** with hydroxylamine by the general method of Worrall⁸ (Scheme 3).

N-arylation of **8a,b** with two equivalent of 2-chloropyrimidine gave the desired N- substituted compounds **9a,b** (Scheme 3). While the formation of **9a,b** appear trivial, the reaction generally proceeded best in the absence of solvent, by heating the required reagent under nitrogen at 130° C for 30 min.

The rearrangement of bis pyrimidylisoxazolones **9a,b** proceeded in refluxing ethanol for 3-12h in the presence of triethylamine or potassium carbonate(Scheme 3).

The mechanism of the rearrangement is consistent with the previous suggestions^{1,9} for the formation of indoles and imidazopyrimidines from isoxazolones under basic conditions. We were unable to find any evidence for the formation of the bis indole (**12**), a plausible alternative product from the presumed penultimate intermediate (**11**) (Scheme 4). Presumably, subtle electron distribution within (**11**) dictates the direction of the final ring forming reaction.



Scheme 4

Conclusion

The base catalysed rearrangements of 3-arylaminoisoxazolones substituted on N-2 with a diazine group appears to be generally applicable to the synthesis of indolaminoimidazopyrimidines, a

class of molecule that has not been previously prepared and because of their multiple H bonding and acceptor sites, could be expected to intercalate with DNA.^{6,7} They would also serve as intermediates for new planar polycyclic heterocycles.

Experimental Section

General procedures. Freshly distilled solvents were used throughout, and anhydrous solvents were dried according to Perrin and Armarego.¹⁰ Melting points were determined on a Philip Harris C4954718 apparatus and are uncorrected. Infrared spectra were recorded on a Thermo Nicolet (Nexus 670) FT-infrared spectrometer, using sodium chloride cells and measured as film or KBr disks. ¹H (300 MHz) and ¹³C (75.5 MHz) NMR measurements were recorded on a Bruker 300 spectrometer in DMSO-d₆, acetone-d₆, CD₂Cl₂ or CDCl₃ using TMS as the internal reference. Mass spectra were recorded on a Varian Matt 311 spectrometer and relative abundances of fragments are quoted in parentheses after the *m/z* values. Microanalyses were performed on a Leco Analyzer 932.

Bis diethyl (1,3-phenylene)thiocarbamoylmalonate (7a). To diethyl malonate (1.58mL, 10.44mmol) in anhydrous THF (20mL) was added sodium (0.24g, 10.44mmol) and the mixture was refluxed under nitrogen for 2h. The solution was cooled to room temperature, 1, 3-phenylenediisothiocyanate (1g, 5.22mmol) was added dropwise, and the resulting yellow solution was stirred at room temperature for 3h. The mixture was extracted with CH₂Cl₂ (4× 20mL) and the aqueous phase was added dropwise to vigorously stirred, ice-cold 1M HCl (10mL), yielding a yellow oil. (2.27g, 85%). ¹H NMR (CDCl₃) δ 1.33 (t, *J*=7.2Hz, 12H), 4.31 (q, *J*=7.2 Hz, 8H), 5.07 (s, 2H), 7.12 (d, *J*=7.2 Hz, 1H), 7.38 (t, *J*=7.8 Hz, 1H), 7.6 (d, *J*=7.8 Hz, 1H), 7.72 (t, *J*=1.5 Hz, 1H), 10.85 (s, 2H); ¹³C NMR (CDCl₃) δ 13.91, 63.16, 67.35, 117.7, 120.11, 122.95, 138.95, 165.62, 187.79; FT-IR (film) ν_{\max} / cm⁻¹: 3269, 2983, 1747, 1600, 1556, 1402, 1306, 1025, 782; Anal. Calcd for C₂₂H₂₈N₂S₂O₈: C, 51.55; H, 5.51; N, 5.47%; Found: C, 51.44; H, 5.12; N, 5.31.

Bis diethyl (2-methyl-1,3-phenylene)thiocarbamoylmalonate (7b). This thiocarbamate was made by the same procedure. Diethyl malonate (1.58mL, 10.44mmol) gave **7b** (2.47g, 90%) as yellow needles, mp 116-117° C. ¹H NMR (CDCl₃) δ 1.35 (t, *J*=7.2 Hz, 12H), 2.83 (s, 3H), 4.32 (q, *J*=7.2 Hz, 8H), 5.15 (s, 2H), 7.34 (t, *J*=7.9 Hz, 1H), 7.56 (d, *J*=8.1 Hz, 2H), 10.55 (s, 2H); ¹³C NMR (CDCl₃) δ 12.43, 13.94, 63.14, 66.64, 125.99, 126.64, 130.97, 138.12, 165.62, 189.84; FT-IR (KBr) ν_{\max} / cm⁻¹: 3271, 2988, 1754, 1720, 1519, 1416, 1309, 1034, 729; Anal. Calcd for C₂₃H₃₀N₂S₂O₈: C, 52.46; H, 5.74; N, 5.32%; Found: C, 51.21; H, 5.38; N, 5.31%.

Bis ethyl 3-(1,3-phenylene)amino-5-oxo-2,5-dihydroisoxazole-4-carboxylate (8a). Hydroxyammonium chloride (0.45g, 7.8mmol) was dissolved in ethanol (8mL)/water (4mL) and then neutralized with potassium hydroxide (0.54g, 7.8mmol).⁸ The filtered solution was added to thiocarbamate **7a** (1g, 1.95mmol) and the mixture was refluxed for 15h before being cooled to room temperature. The reaction mixture was quenched with 1M HCl (10mL), yielding a cream

precipitate. The precipitate was recrystallised from ethanol to give **8a** (0.56g, 70%) as cream crystals, mp 214° C dec. ¹H NMR (DMSO-d₆) δ 1.25 (t, *J*=7.2 Hz, 6H), 4.2 (q, *J*=7.2 Hz, 4H), 7.14 (dd, *J*₁= 8.1Hz, *J*₂=4.5Hz, 2H), 7.37 (t, *J*=7.8 Hz, 1H), 7.44 (t, *J*=1.8 Hz, 1H), 9.32 (s, 2H); ¹³C NMR (DMSO-d₆) δ 14.93, 59.46, 73.82, 114.07, 117.34, 130.62, 138.38, 162.62, 164.74, 167.19; FT-IR (KBr) ν_{\max} / cm⁻¹: 3171, 1778, 1722, 1672, 1618, 1582, 1314, 1183, 1015, 789; MS *m/z* (%) 418(M⁺,15), 368(7), 210(16), 159(16), 132(30), 114(48), 83(84), 45(100).

Bis ethyl 3-(2-methyl-1,3-phenylene)amino-5-oxo-2,5-dihydroisoxazole-4-carboxylate (8b).

This compound was prepared by the same procedure. Thiocarbamate **7b** (1g, 1.9mmol) gave **8b** (0.66g, 80%) as cream solid, mp 154-157° C. ¹H NMR (Acetone-d₆) δ 1.31 (t, *J*=6.9 Hz, 6H), 2.37 (s, 3H), 4.29 (q, *J*=6.9 Hz, 4H), 7.3 (t, *J*=8.1 Hz, 1H), 7.47 (d, *J*=7.5 Hz, 2H), 9.35 (s, 2H); ¹³C NMR (Acetone -d₆) δ 11.89, 13.90, 59.43, 74.41, 123.45, 125.57, 135.86, 164.97, 165.07, 165.47; FT-IR (KBr) ν_{\max} / cm⁻¹: 3448, 2988, 1712, 1673, 1597, 1433, 795; Anal. Calcd for C₁₉H₂₀N₄O₈: C, 52.78; H, 4.66; N, 12.96%; Found: C, 52.65; H, 4.22; N, 12.88%.

Bis ethyl 3-(1,3-phenylene)amino-2-(pyrimidin-2-yl)-5-oxo-2,5-dihydroisoxazole-4-carboxylate (9a).

Isoxazolone **8a** (0.5g, 1.19mmol) and 2-chloropyrimidine (0.272g, 2.38mmol) were heated neat under nitrogen at 130° C for 30 min. The resulting product was recrystallised from ethanol to give the isoxazolone **9a**(0.446g, 65%) as brown crystals mp 162-164° C. ¹H NMR (DMSO-d₆) δ 1.15 (t, *J*=7.2 Hz, 6H), 4.1 (q, *J*=7.2 Hz, 4H), 6.85 (d, *J*=7.2 Hz, 2H), 6.94 (t, *J*=6.6 Hz, 1H), 7.21 (s, 1H), 7.4 (t, *J*=5.1 Hz, 2H), 8.7 (d, *J*=4.8 Hz, 4H), 10.33 (s, 2H); ¹³C NMR (DMSO-d₆) δ 14.62, 60.29, 78.99, 116.8, 119.21, 120.8, 129.4, 138.49, 156.59, 159.78, 161.36, 162.71, 164.02; FT-IR (KBr) ν_{\max} / cm⁻¹: 3435, 2925, 1774, 1696, 1663, 1594, 1398, 1177, 1026, 779; MS *m/z* (%) 574(M⁺,8), 530(31), 486(79), 440(37), 394(100), 365(86), 323(100), 277(100), 261(58), 205(62), 145(79), 89(100), 459(100).

Bis ethyl 3-(2-methyl-1,3-phenylene)amino-2-(pyrimidin-2-yl)-5-oxo-2,5-dihydroisoxazole-4-carboxylate (9b).

This compound was prepared by the same procedure. Isoxazolone **8b** (0.5g, 1.16mmol) gave **9b** (0.476g, 70%) as brown crystals, mp 192-194° C. ¹H NMR (CDCl₃) δ 1.35 (t, *J*=7.2 Hz, 6H), 2.48 (s, 3H), 4.3 (q, *J*=7.2 Hz, 4H), 6.71 (t, *J*=6.9 Hz, 1H), 6.9 (d, *J*=8.1 Hz, 2H), 7.12 (t, *J*=4.8 Hz, 2H), 8.56 (d, *J*=4.5 Hz, 4H), 10.13 (s, 2H); ¹³C NMR (CDCl₃) δ 13.10, 14.40, 60.85, 78.95, 119.09, 120.40, 125.78, 126.14, 137.36, 155.94, 158.52, 161.23, 163.31, 164.45; FT-IR (KBr) ν_{\max} / cm⁻¹: 3438, 2977, 1773, 1710, 1663, 1600, 1577, 1397, 1215, 779; Anal. Calcd for C₂₇H₂₄N₈O₈: C, 55.10; H, 4.11; N, 19.04%; Found: C, 49.95; H, 4.22; N, 19.00%.

Ethyl 2-[3-ethoxycarbonyl-2-(pyrimidin-2-ylamino)indol-6-yl]aminoimidazo[1,2-a]pyrimidine-3-carboxylate (10a).

The isoxazolone **9a** (0.1g, 0.174mmol) and triethylamine (0.2mL) were refluxed in ethanol (10mL) for 3h. On cooling, **10a** crystallized as a cream solid (0.072g, 85%) mp 205-207° C. ¹H NMR (DMSO-d₆) δ 1.17 (t, *J*=7 Hz, 3H), 1.41 (t, *J*=7 Hz, 3H), 4.13 (q, *J*=7 Hz, 2H), 4.43 (q, *J*=7 Hz, 2H), 6.81 (d, *J*=7.8 Hz, 1H), 7.13 (t, *J*=8.1 Hz, 1H), 7.27 (t, *J*=4.2 Hz, 1H), 7.37 (t, *J*=4.5 Hz, 1H), 7.52 (d, *J*=7.8 Hz, 1H), 7.77(s, 1H), 8.61(bs, 1H), 8.72(d, *J*=4.5 Hz, 3H), 9.29(bs, 1H), 10.39(bs, 1H); ¹³C NMR (DMSO-d₆) δ 14.64, 14.89, 60.19, 60.82, 78.32, 96.48, 110.88, 113.64, 116.12, 116.78, 120.88, 129.53, 136.04, 138.28, 140.95,

148.89, 152.47, 154.38, 157.07, 159.82, 160.77, 162.38, 162.96, 164.32; FT-IR (KBr) ν_{\max} / cm^{-1} : 3399, 2990, 1779, 1664, 1614, 1584, 1395, 1176, 1096, 761; MS m/z (%) 486(M^+ , 83), 485(100), 440(41), 392(63), 365(69), 205(55), 79(84), 78(100).

Ethyl 2-[3-ethoxycarbonyl-7-methyl-2-(pyrimidin-2-ylamino)indol-6-yl]aminoimidazo[1,2-a]pyrimidine-3-carboxylate (10b). This compound was prepared by the same procedure. The isoxazolone **9b** (0.1g, 0.17mmol) gave **10b** (0.061g, 72%) as cream solid, mp 230° C dec. ^1H NMR (CD_2Cl_2) δ 1.32 (t, $J=6.9$ Hz, 3H), 1.53 (t, $J=7.2$ Hz, 3H), 2.44 (s, 3H), 4.27 (q, $J=6.9$ Hz, 2H), 4.55 (q, $J=7.2$ Hz, 2H), 6.9 (d, $J=7.7$ Hz, 1H), 7.06 (d, $J=4.5$ Hz, 1H), 7.08 (t, $J=4.5$ Hz, 1H), 7.12 (t, $J=4.8$ Hz, 1H), 8.38 (d, $J=7.7$ Hz, 1H), 8.57 (d, $J=4.8$ Hz, 3H), 9.31 (bs, 1H), 10.08 (s, 1H); ^{13}C NMR (CD_2Cl_2) δ 12.33, 14.09, 14.53, 60.54, 60.82, 78.05, 96.65, 109.6, 112.37, 117.73, 117.93, 119.30, 121.32, 126.65, 135, 136.4, 139.34, 151.32, 156.15, 158.45, 162.03; FT-IR (KBr) ν_{\max} / cm^{-1} : 3407, 2982, 1781, 1686, 1583, 1480, 1396, 1103, 1039, 776; Anal. Calcd for $\text{C}_{25}\text{H}_{24}\text{N}_8\text{O}_4$: C, 59.99; H, 4.83; N, 22.39%; Found: C, 59.54; H, 4.39; N, 22.23%.

Acknowledgements

We are grateful to professor R.H.Prager (Flinders University) for his valuable comments and gift of chemicals. We also thank Urmia University for financial support.

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