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Note

Synthesis of hexahydro-1,3,5-triazines: A new approach from N-substituted-α-aminoisothiocyanates

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Azomethines **1a-m** react with ammonium thiocyanate/acetic acid to give the corresponding N-substituted-α-aminoisothiocyanates **2a-m** which are found to be excellent starting materials for the synthesis of hexahydro-1,3,5-triazines **3a-m**. Compounds **2a-m** on treatment with toluene-2,4-diisocyanate give the corresponding hexahydro-1,3,5-triazines **3a-m** in good yields.

Keywords: Triazines, azomethines, ammonium thiocyanate, thiocyanic acid

IPC: **Int.Cl.**[7] **C 07 C, C 07 D**

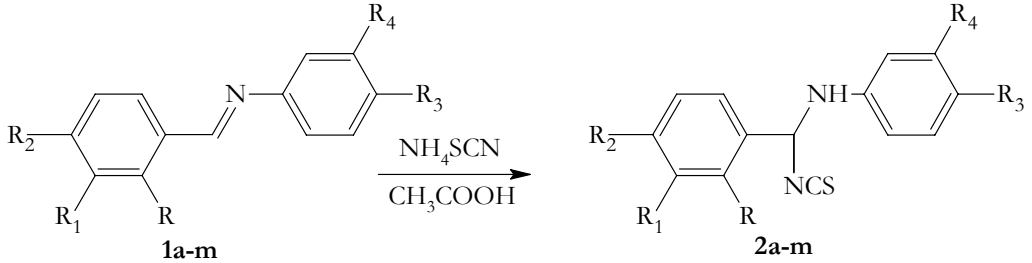
Hexahydro-1,3,5-triazines have been prepared previously by the reaction of organic isocyanates and isothiocyanates with thiourea[1-3], alkali metal cyanates[4], amidines[5], imines[6,7], enamines[8] and imidates[9]. Solvent-free preparation of tris-pyrazoliy-1,3,5-triazines[10] as well as various camphor derived oxazolineazomethine imines[11] and the synthesis of solution phase combinatorial library of 4,6-diamino-1,2-dihydro-1,3,5-triazines[12] were reported recently. Moreover, sequential aza-Wittig/cycloaddition/ring-transformation reactions leading to one-pot synthesis of novel 1,3,5 triazine derivatives[13] are also known. In this paper, we report the synthesis of hexahydro-1,3,5-triazines **3a-m** from the reaction of N-substituted-α-aminoisothiocyanates **2a-m** with toluene-2,4-diisocyanate. N-substituted-α-amino-isothiocyanates **2a-m** were obtained by the addition of ammonium thiocyanate/acetic acid to azomethines **1a-m**.

Results and Discussion

N-substituted-α-aminoisothiocyanates **2a-m** can be prepared in excellent yields (80-100%) on addition of ammonium thiocyanate in one lot to a stirred solution of azomethines **1a-m** in acetic acid **(Scheme I).** The structural assignment of **2a-m** is based primarily on spectral data. The IR spectra of **2a-m** exhibit the strong absorption assignable to –NCS group at 2050 cm^{-1}. The elemental analysis was also consistent with the assigned structure **(Table I)**.

Toluene-2,4-di(arylalkyl)-6-thioxo-1,3,5-triazinan-2-one derivatives **3a-m** were obtained in moderate to excellent yields from the reaction of **2a-m** with toluene-2,4-diisocyanate in dry THF at reflux temperature **(Scheme II).** Dropwise addition of toluene-2,4-diisocyanate and the use of dry THF as the solvent are indispensable in these reactions. When toluene-2,4-diisocyanate was added in one portion or the reaction was performed in solvents such as benzene or chloroform, the yields of triazines **3a-m** came down drastically and large amounts of the corresponding isocyanate trimers were obtained.

The structural assignment of **3a-m** is based primarily on spectral data. The IR spectra exhibit the absorptions assignable to -NH, >C=O and >C=S groups at 3260-80, 1710, 1590 and 1340-1320 cm^{-1} respectively. In the ^1H NMR spectra of the triazines **3a-m**, the –NH-C=S proton signals were obtained around δ12.1-12.4, which disappeared on D_2O exchange. A prominent singlet for the methyl group of toluene-2,4-diisocyanate was observed around δ 2.2-2.35 in case of all the compounds **3a-m**. The elemental analysis was found to be consistent with the structures assigned **(Table II)**. The mass spectra



1a-m **2a-m**

Scheme I

Table I — Characterization data of compounds **2a-m**

Compd	R	R^1	R^2	R^3	R^4	Yield (%)	m. p. °C	Mol. formula	Found % (Calcd) C	H	N
2a	H	H	OCH_3	H	H	92	145	$C_{15}H_{14}N_2OS$	66.5 (66.7	5.2 5.2	10.3 10.4)
2b	H	H	OCH_3	H	Cl	94	172	$C_{15}H_{13}N_2OSCl$	59.1 (59.1	4.2 4.3	9.2 9.2)
2c	H	OCH_3	OCH_3	OCH_3	H	96	152	$C_{17}H_{18}N_2O_3S$	61.8 (61.9	5.5 5.5	8.6 8.4)
2d	H	OCH_3	OCH_3	OCH_3	Cl	91	133	$C_{17}H_{17}N_2O_3SCl$	60.0 (55.9	4.6 4.6	7.7 7.6)
2e	H	H	H	H	H	83	160	$C_{14}H_{12}N_2S$	69.9 (70.0	5.1 5.0	11.6 11.6)
2f	H	H	H	H	Cl	90	173	$C_{14}H_{11}N_2SCl$	61.1 (61.3	4.0 4.0	10.2 10.1)
2g	CH_3	H	CI	H	H	94	140	$C_{15}H_{13}N_2SCl$	62.7 (62.5	4.4 4.5	9.6 9.7)
2h	CH_3	H	H	H	H	92	158	$C_{15}H_{14}N_2S$	70.7 (70.8	5.4 5.5	11.0 11.0)
2i	CH_3	H	OCH_3	H	Cl	86	212	$C_{16}H_{15}N_2OSCl$	60.1 (60.2	4.8 4.7	8.7 8.7)
2j	CH_3	H	Cl	H	Cl	89	224	$C_{15}H_{12}N_2SCl_2$	55.5 (55.7	3.6 (3.7	8.9 8.6)
2k	CH_3	H	CH_3	H	Cl	90	218	$C_{16}H_{15}N_2SCl$	63.6 (63.4	4.8 4.9	9.1 9.2)
2l	CH_3	H	H	H	Cl	91	208	$C_{15}H_{10}N_2SCl$	63.0 (63.0	3.7 3.5	9.7 9.8)
2m	H	CH_3	H	H	H	85	175	$C_{15}H_{14}N_2S$	70.6 (70.8	5.4 5.5	11.1 11.0)

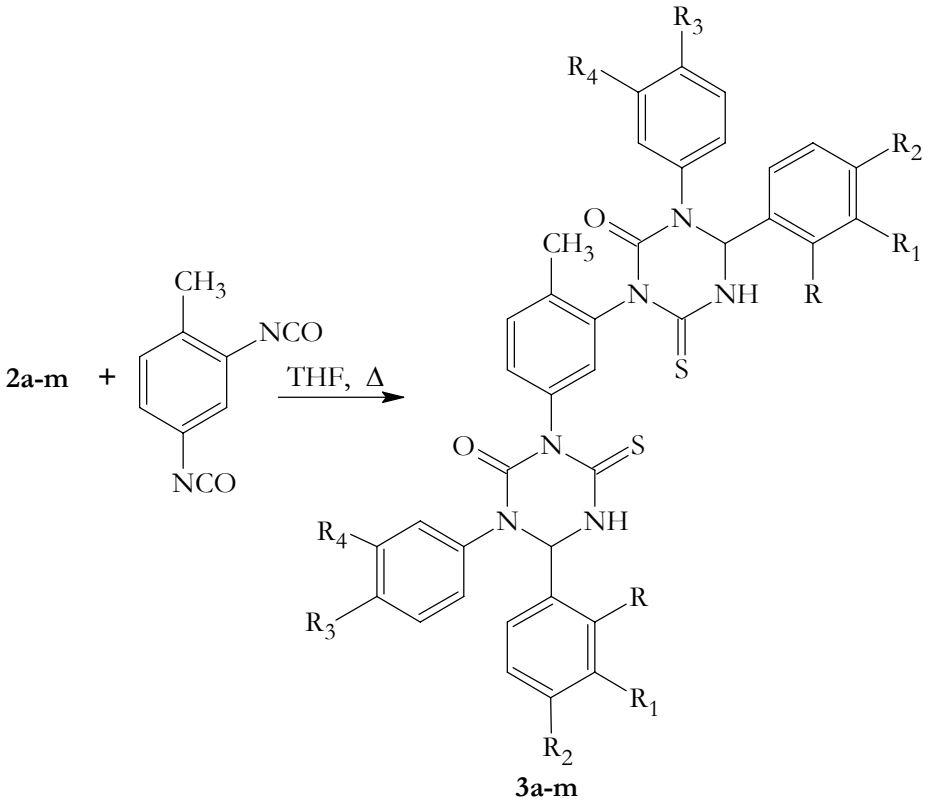
Table II — Characterization data of compounds **3a-m**

Compd	R	R^1	R^2	R^3	R^4	Yield (%)	m. p. ^{0}C	Mol. formula	Found % (calcd) C	H	N	^{1}H NMR ($CDCl_3$) δ ppm
3a	H	H	OCH_3	H	H	52	132	$C_{39}H_{34}N_6O_4S_2$	65.7 (65.5	4.7 4.7	11.8 11.7)	2.3, bs (3H), 7.1-7.9, m (3H), 6.9, bs (2H), 12.2, bs (2H), 7.0-7.2, m (10H), 4.25, s (6H), 7.1-7.3, m (8H)
3b	H	H	OCH_3	H	Cl	65	225	$C_{39}H_{32}N_6O_4S_2Cl_2$	60.0 (59.8	3.8 4.0	10.6 10.7)	2.2, bs (3H), 7.15-7,.m (3H), 6.1, bs (2H), 12.3, bs (2H), 7.0-7.2, m (8H), 4.2, s (6H), 7.1-7.25, m (8H)
3c	H	OCH_3	OCH_3	OCH_3	H	51	170	$C_{43}H_{42}N_6O_8S_2$	61.7 (61.8	5.0 5.0	10.2 10.0)	2.25, bs (3H), 7.2-7.8, m (3H), 6.0, bs (2H), 12.2, bs (2H), 7.15-7.8, m (8H), 4.3, s (18H), 7.1-7.3, m (6H),
3d	H	OCH_3	OCH_3	OCH_3	Cl	60	177	$C_{43}H_{40}N_6O_8S_2Cl_2$	57.2 (57.1	4.4 4.4	9.5 9.3)	2.28, bs (3H), 7.2-7.9, m (3H), 6.2, bs (2H), 12.3, bs (2H), 7.2-7.9, m (6H), 4.32, s (18H), 7.2-7.9, m (6H)
3e	H	H	H	H	H	53	165	$C_{37}H_{30}N_6O_2S_2$	67.7 (67.8	4.4 4.5	12.7 12.8)	2.35, bs (3H), 7.0-7.9, m (3H), 6.0, bs (2H), 12.25, bs (2H), 7.2-7.9, m (10H), 7.2-7.9, m (10H)

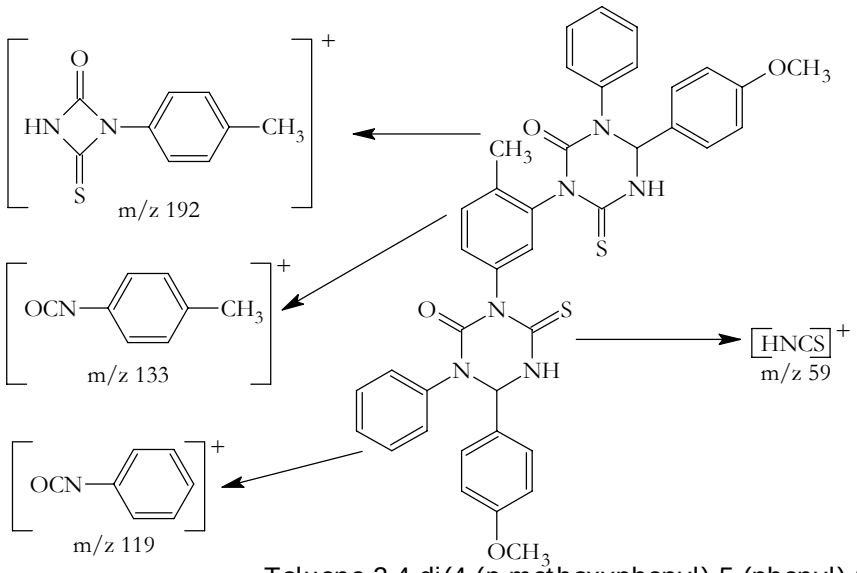
— Contd

Table II — Characterization data of compounds **3a-m** — *Contd*

Compd	R	R^1	R^2	R^3	R^4	Yield (%)	m. p. ^{0}C	Mol. formula	Found % (calcd) C	H	N	^{1}H NMR ($CDCl_3$) δ ppm
3f	H	H	H	H	Cl	58	154	$C_{37}H_{28}N_6O_2S_2Cl_2$	61.4 (61.4	3.7 3.8	11.7 11.6)	2.30, bs (3H), 7.1-7.85, m (3H), 6.1, bs (2H), 12.25, bs (2H), 7.2--6, m (8H), 7.0-7.3, m (10H)
3g	CH_3	H	CI	H	H	57	168	$C_{39}H_{32}N_6O_2S_2Cl_2$	62.7 (62.31	4.5 4.26	11.2 11.1)	2.30, bs (9H), 7.0-7.9, m (3H), 6.2, bs (2H), 12.30, bs (2H), 7.0-7.6, m (10H), 7.0-7.3, m (6H)
3h	CH_3	H	H	H	H	48	140	$C_{39}H_{34}N_6O_2S_2$	69.1 (68.6	4.3 4.9	12.2 12.3)	2.30, bs (9H), 7.1-7.8, m (3H), 6.20, bs (2H), 12.30, bs (2H), 7.1-7.6, m (10H), 7.1-7.6, m (8H)
3i	CH_3	H	OCH_3	H	Cl	41	273	$C_{41}H_{36}N_6O_4S_2Cl_2$	60.6 (60.6	4.2 4.4	10.4 10.3)	2.25, bs (9H), 7.2-7.9, m (3H), 6.20, bs (2H), 12.20, bs (2H), 7.2-6.5, m (8H), 4.30 s (6H), 7.1-7.3, m (6H)
3j	CH_3	H	Cl	H	Cl	53	280	$C_{39}H_{36}N_6O_2S_2Cl_4$	56.8 (56.6	4.2 4.3	10.0 10.1)	2.20, bs (9H), 7.1-7.85, m (3H), 6.25, bs (2H),12.25, bs (2H), 7.1-7.5, m (8H), 7.1-7.85, m (6H)
3k	CH_3	H	CH_3	H	Cl	58	235	$C_{41}H_{36}N_6O_2S_2Cl_2$	63.0 (63.1	4.3 4.6	10.6 10.7)	2.30, bs (15H), 7.10-7.8, m (3H), 6.20, bs (2H), 12.25, bs (2H), 7.0-7.75, m (8H), 7.1-7.5, m (6H)
3l	CH_3	H	H	H	Cl	50	230	$C_{39}H_{32}N_6O_2S_2Cl_2$	62.5 (62.3	4.1 4.2	11.0 11.1)	2.25, bs (9H), 7.0-7.9, m (3H), 6.30, bs (2H), 12.20, bs (2H), 7.0-7.65, m (8H), 7.0-7.5, m (8H)
3m	H	CH_3	H	H	H	60	196	$C_{39}H_{34}N_6O_2S_2$	68.4 (68.6	4.9 4.9	12.4 12.3)	2.26, bs (9H), 7.0-7.8, m (3H), 6.25, bs (2H), 12.20, bs (2H), 7.6, m (8H), 7.0-7.5, m (8H)

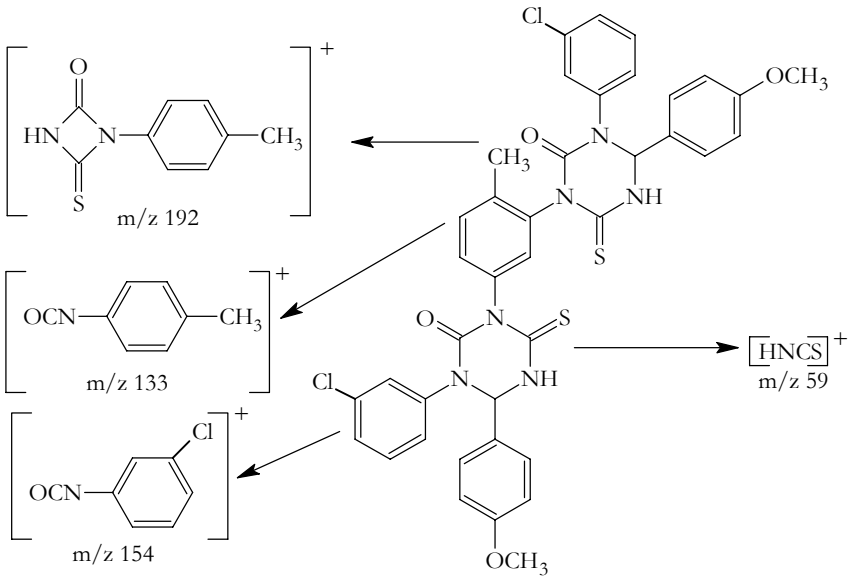


Scheme II



Toluene-2,4-di(4-(*p*-methoxyphenyl)-5-(phenyl)-6 -thioxo-1,3,5-triazinan-2-one **3a**

Scheme III



Toluene-2,4-di(4-(*p*-methoxyphenyl)-5-(*m*-chloro phenyl)-6-thioxo-1,3,5-triazinan-2-one **3b**

Scheme IV

showed weak molecular ion peaks because these triazines **3a-m** are very easily susceptible to fragmentation under electron impact. The results are in agreement with those obtained previously in case of hexahydro-1,3,5-triazines[14,15]. Mass spectra of toluene-2,4-di(4-(*p*-methoxyphenyl),-5-(*m*-chlorophenyl))-6-thioxo-1,3,5-triazinan-2-one **3b**, showed peaks at m/z 133, 59,192 and 154. However, toluene-2,4-di(4-(*p*-methoxyphenyl),-5-(phenyl))-6-thioxo-1,3,5-triazinan-2-one **3a**, showed peaks at m/z 133,59,192 and 119. The fragmentation patterns of **3a** and **3b** are shown in **Schemes III** and **IV** respectively.

Other common features noted in the fragmentation pattern of **3a-m** are, loss of fragments of m/z 133(Path-a) and 59(Path-b), 192 (Path-c) and the fragment whose mass depends upon the substitution at the N-aryl ring. For example, in case of toluene-2,4-

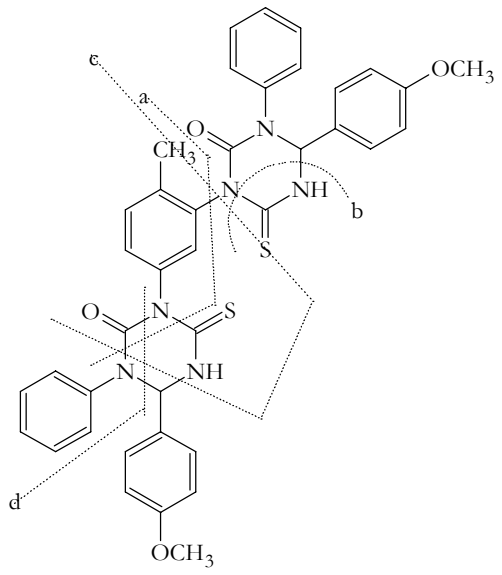
di(4-(*p*-methoxyphenyl),-5-(*m*-chlorophenyl)-6-thioxo-1,3,5-triazinan-2-one **3b**, where N-aryl ring is substituted by chlorine, fragment m/z 154 is obtained (Path-d), whereas in case of toluene-2,4-di(4-(*p*-methoxyphenyl),-5-(phenyl))-6-thioxo-1,3,5-triazinan-2-one **3a**, where there is no substitution on the N-aryl ring, fragment of m/z 119 is obtained (Path-d) **(Scheme V)** which clearly supports the assigned structures.

The possible general mechanism for the formation of hexahydro-s-triazines **3a-m** from various N-substituted-α-amino isothiocyanates **2a-m** and toluene-2,4-diisocyanate is described in **Scheme VI**.

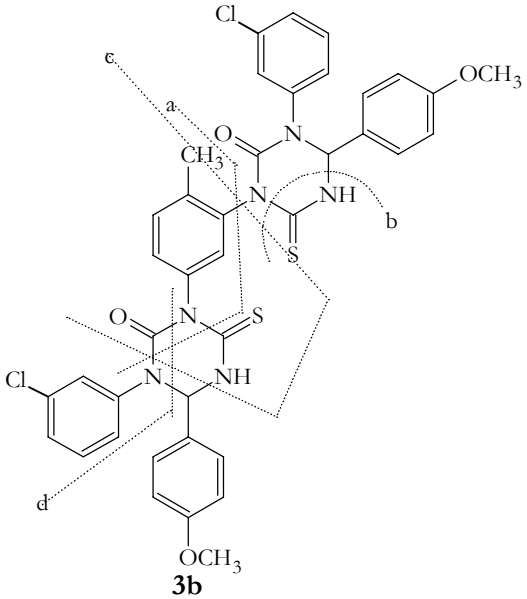
In conclusion, N-substituted-α-aminoisothiocyanates, which can be easily prepared by the addition of ammonium thiocyanate/acetic acid (thiocyanic acid) to an equimolar mixture of aromatic carbonyl compounds and aromatic amines were found to be useful starting materials for the synthesis of hexahydro-1,3,5-triazine derivatives. The chief advantage of this method over the other existing methods is that α-aminoisothiocyanates are obtained in isolable quantitative yields, and their further reaction with toluene-2,4-diisocyanate produces excellent yields of triazines with no other side products unlike in some other cases[6,7].

Experimental

Melting points were determined in open capillary

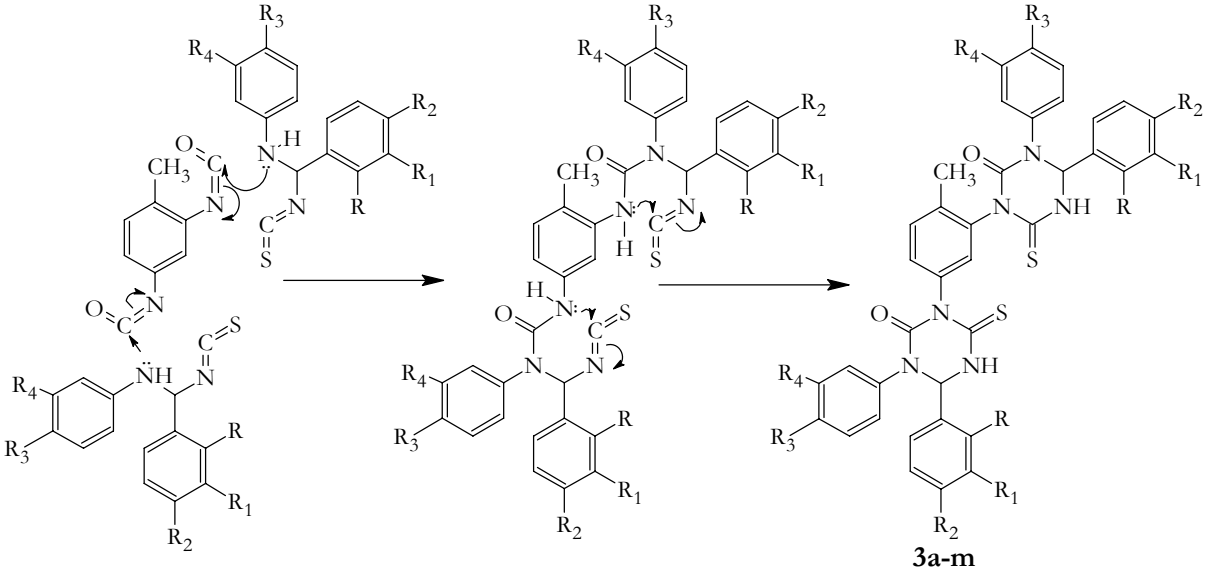


3a



3b

Scheme V



3a-m

Scheme VI

tubes in sulphuric acid bath and are uncorrected. Infrared spectra were recorded in KBr pellets on a Perkin-Elmer spectrophotometer and ^{1}H NMR spectra on a EM-390, 90MHz NMR spectrometer using tetramethylsilane (TMS) as internal standard. The homogeneity of compounds was checked by TLC on silica-gel G plates and spots were located in iodine vapour chamber.

General procedure for the synthesis of N-substituted-α-aminoisothiocyanates 2a-m from azomethines 1a-m.

To a stirred solution of **1a-m** (0.01 mole) in glacial acetic acid was added ammonium thiocyanate (0.015 mole) in one lot. After stirring for 30 min, N-substituted-α–aminoisothiocyanate **2a-m** separated out which was filtered, washed with water, dried and purified by recrystallization from ethanol or ethanol-THF mixture **(Table I)**.

General procedure for the synthesis of toluene-2,4-di(arylalkyl)-6-thioxo-1,3,5-triazinan-2-one derivatives 3a-m from 2a-m

A solution of toluene-2,4-diisocyanate (0.005 mole) in THF was added dropwise to a solution of N-substituted-α-aminoisothiocyanate **2a-m** (0.01mole) in THF at reflux temperature. The reaction mixture was refluxed for 4-5 hr. The solvent was evaporated to give **3a-m**, which was filtered and purified by recrystallization from MeOH-THF mixture. The ^{1}H NMR data for **3a-m** is shown in **Table II**.

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