Synthesis of 1-Aryl-2-amino/anilino-4-phenyl-1,6-dihydro-1,3,5-triazine-6-thione and Related Thioureas

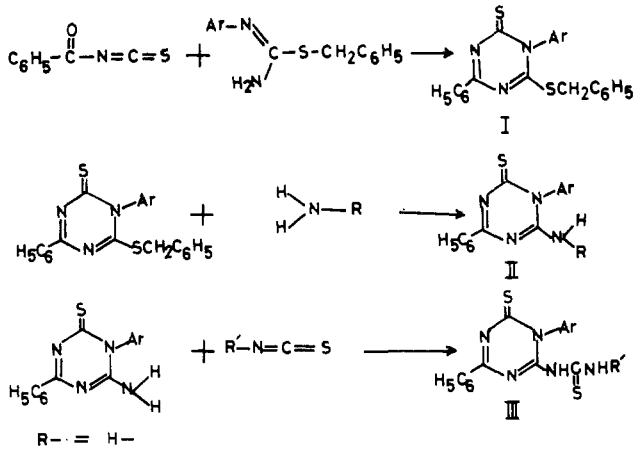
Ramesh Chandra and Pramod K. Srivastava*

Department of Chemistry, Banaras Hindu University, Varanasi 221005, India

Different 1-aryl-2-(benzylmercapto)-4-phenyl-1,6-dihydro-1,3,5-triazine-6-thiones have been synthesized by known methods. These triazines on treatment with ammonia/amines under suitable conditions afforded corresponding 2-amino/anilino derivatives. 1-Aryl-2-amino-4-phenyl-1,6-dihydro-1,3,5-triazine-6-thione on interaction with isothiocyanates gave related thioureas.

The presence of antituberculous (*1*, *2*), antithyroidal (*3*), and antitumor (*4*) activity in some disubstituted thiocarbamides led us to search for new members of this series containing the triazinyl moiety.

The present communication deals with the synthesis of 1-aryl-2-amino/anilino-4-phenyl-1,6-dihydro-1,3,5-triazine-6-thione (II) and *N*-(1-aryl-4-phenyl-1,6-dihydro-6-thioxo-1,3,5-triazinyl)-*N'*-arylthiourea (III); the precursor 1-aryl-2-(benzylmercapto)-4-phenyl-1,6-dihydro-1,3,5-triazine-6-thione (I) was obtained by condensation of benzoyl isothiocyanate (*5*) and *S*-benzyl-*N*-arylisothiourea (*6*). The amino/anilinotriazines (II) were obtained in excellent yields when equimolecular quantities of triazines (I) and ammonia/amines were refluxed for a period of 9–10 h. The aminotriazines (II) when reacted with isothiocyanates afforded related thioureas (III) (*1–3*, *7*).



Experimental Procedure

Melting points were determined with a Kofler hot stage apparatus and are uncorrected.

2-(Benzylmercapto)-1,4-diphenyl-1,6-dihydro-1,3,5-triazine-6-thione (I) (8–11). A solution of benzoyl isothiocyanate (6.5 g, 40 mmol) was added dropwise with vigorous stirring to *S*-benzyl-*N*-phenylisothiourea (9.7 g, 40 mmol) in acetone (50 mL) over a period of 5 min. A golden yellow solid separated which was recrystallized with benzene: yield 10.4 g (70%); mp 186 °C; IR (Nujol) 1080 (C=S), 1635 (C=N), 670 (C—S—C) cm^{-1}; NMR ($CDCl_3$) δ 4.525 (s, 2 H, CH_2), 7.208–7.881 (m, 15 H, Ar*H*). By adoption of a similar procedure 2-(benzylmercapto)-1-(*p*-chlorophenyl)-4-phenyl-1,6-dihydro-1,3,5-triazine-6-thione was prepared: yield 75%; mp 215 °C.

Table I. 2-Amino/anilino-1-aryl-4-phenyl-1,6-dihydro-1,3,5-triazine-6-thione[a]

Ar	R	mp, °C	yield, %
C_6H_5	H	233	80
C_6H_5	C_6H_5	248	68
C_6H_5	*o*-$CH_3C_6H_4$	193	65
C_6H_5	*m*-$CH_3C_6H_4$	199	65
C_6H_5	*p*-$CH_3C_6H_4$	195	60
C_6H_5	*o*-$CH_3OC_6H_4$	176	55
C_6H_5	*p*-$CH_3OC_6H_4$	179	55
C_6H_5	*p*-ClC_6H_4	217	70
C_6H_5	$C_6H_5CH_2$	157	75
C_6H_5	*n*-C_4H_9	71	55
p-ClC_6H_4	H	223	90
p-ClC_6H_4	C_6H_5	204	84
p-ClC_6H_4	*m*-$CH_3C_6H_4$	246	80
p-ClC_6H_4	*p*-$CH_3C_6H_4$	231	85
p-ClC_6H_4	*o*-$CH_3OC_6H_4$	196	65
p-ClC_6H_4	*p*-$CH_3OC_6H_4$	242	65
p-ClC_6H_4	*m*-ClC_6H_4	206	75
p-ClC_6H_4	*p*-ClC_6H_4	229	70
p-ClC_6H_4	$C_6H_5CH_2$	291	60
p-ClC_6H_4	*n*-C_4H_9	74	55

[a] All of these compounds gave elemental analysis (C, H, N, S) within ±0.30 of calculated values.

2-Anilino-1,4-diphenyl-1,6-dihydro-1,3,5-triazine-6-thione (II). 2-(Benzylmercapto)-1,4-diphenyl-1,6-dihydro-1,3,5-triazine-6-thione (7 g, 18 mmol) was dissolved in absolute alcohol (80 mL). Distilled aniline (2 g, 20 mmol) was added to it and the reaction mixture was refluxed for 9 h, cooled, and left overnight. A yellow shining product separated which was recrystallized with alcohol: yield 4.35 g (68%); mp 248 °C; IR (Nujol) 3340 (NH), 1635 (C=N), 1080 (C=S) cm^{-1}; NMR ($CDCl_3$) δ 3.80 (s, 1 H, N*H*), 7.316–7.85 (m, 15 H Ar*H*). Similarly other amines were used and the details are recorded in Table I.

2-Amino-1,4-diphenyl-1,6-dihydro-1,3,5-triazine-6-thione (II). 2-(Benzylmercapto)-1,4-diphenyl-1,6-dihydro-1,3,5-triazine-6-thione (5 g, 13 mmol) was refluxed with alcohol (50 mL) saturated with ammonia on an oil bath with constant stirring for a period of 6 h. Alcoholic ammonia was added in fractions (10 mL) throughout the course of the reaction to keep the reaction mixture ammoniacal. After the solution was cooled, a light yellow solid separated which was washed with petroleum ether and recrystallized with alcohol: yield 3.18 g (80%); mp 233 °C; IR (Nujol) 3480, 3360 (NH_2), 1635 (C=N), 1080 (C=S) cm^{-1}.

N-(1,4-Diphenyl-1,6-dihydro-6-thioxo-1,3,5-triazinyl)-N'-methylthiourea (III). 2-Amino-1,4-diphenyl-1,6-dihydro-1,3,5-triazine-6-thione (1.4 g, 5 mmol) was mixed with methyl isothiocyanate (0.5 g), heated on a water bath for a period of 45 min, and then cooled and washed with petroleum ether. The compound thus obtained was recrystallized with alcohol into shining yellow crystals: yield 1.73 g (92%); mp 157 °C; IR (Nujol) 3290 (NH), 1635 (C=N), 1080 (C=S), 1170 cm^{-1} (NC(=S)N). Similarly other isothiocyanates were used and the

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Table II. *N*-(1-Aryl-4-phenyl-1,6-dihydro-1,3,5-triazinyl)-*N'*-arylthiourea[a]

Ar	R'	mp, °C	yield, %
C_6H_5	CH_3	157	92
C_6H_5	C_2H_5	182	85
C_6H_5	n-C_4H_9	239	63
C_6H_5	C_6H_5	241	80
C_6H_5	o-$CH_3C_6H_4$	213	85
C_6H_5	p-$CH_3C_6H_4$	246	90
C_6H_5	o-$CH_3OC_6H_4$	219	80
C_6H_5	p-$CH_3OC_6H_4$	251	86
C_6H_5	p-$C_2H_5OC_6H_4$	197	65
C_6H_5	o-ClC_6H_4	224	88
p-ClC_6H_4	CH_3	162	95
p-ClC_6H_4	C_2H_5	229	85
p-ClC_6H_4	n-C_4H_9	239	75
p-ClC_6H_4	C_6H_5	234	85
p-ClC_6H_4	o-$CH_3C_6H_4$	237	80
p-ClC_6H_4	p-$CH_3C_6H_4$	232	84
p-ClC_6H_4	o-$CH_3OC_6H_4$	236	75
p-ClC_6H_4	o-$C_2H_5OC_6H_4$	243	65
p-ClC_6H_4	p-$C_2H_5OC_6H_4$	241	68
p-ClC_6H_4	o-ClC_6H_4	231	85

[a] All of these compounds gave elemental analysis (C, H, N, S) within ±0.30 of the calculated values. These compounds are submitted for review.

details are recorded in Table II.

Acknowledgment

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Registry No. I(Ar = Ph), 39543-11-8; I(Ar = C_6H_4-*p*-Cl), 15998-34-2; II(Ar = Ph, R = H), 84119-18-6; II(Ar = R = Ph), 83490-26-0; II(Ar = Ph, R = C_6H_4-*o*-Me), 84119-19-7; II(Ar = Ph, R = C_6H_4-*m*-Me), 84119-20-0; II(Ar = Ph, R' = C_6H_4-*p*-Me), 84119-21-1; II (Ar = Ph, R = C_6H_4-*o*-OMe), 84119-22-2; II(Ar = Ph, R = C_6H_4-*p*-OMe), 84119-23-3; II(Ar = Ph, R = C_6H_4-*p*-Cl), 84119-24-4; II(Ar = Ph, R = CH_2-Ph), 84119-25-5; II(Ar = Ph, R = Bu), 84119-26-6; II(Ar = C_6H_4-*p*-Cl, R = H), 84119-27-7; II(Ar = C_6H_4-*p*-Cl, R = Ph), 84119-28-8; II(Ar = C_6H_4-*p*-Cl, R = C_6H_4-*m*-Me), 84119-29-9; II(Ar = C_6H_4-*p*-Cl, R = C_6H_4-*p*-Me), 84119-30-2; II(Ar = C_6H_4-*p*-Cl, R = C_6H_4-*o*-OMe), 84119-31-3; II(Ar = C_6H_4-*p*-Cl, R = C_6H_4-*p*-OMe), 84119-32-4; II(Ar = C_6H_4-*p*-Cl, R = C_6H_4-*m*-Cl), 84119-33-5; II(Ar = R = C_6H_4-*p*-Cl), 84119-34-6; II(Ar = C_6H_4-*p*-Cl, R = CH_2-Ph), 84119-35-7; II(Ar = C_6H_4-*p*-Cl, R = Bu), 84119-36-8; III(Ar = Ph, R' = Me), 84119-37-9; III(Ar = Ph, R' = Et), 84119-38-0; III(Ar = Ph, R' = Bu), 84119-39-1; III(Ar = R' = Ph), 84119-40-4; III(Ar = Ph, R' = C_6H_4-*o*-Me), 84119-41-5; III(Ar = Ph, R' = C_6H_4-*p*-Me), 84119-42-6; III(Ar = Ph, R' = C_6H_4-*o*-OMe), 84130-11-0; III(Ar = Ph, R' = C_6H_4-*p*-OMe), 84119-43-7; III(Ar = Ph, R' = C_6H_4-*p*-OEt), 84119-44-8; III(Ar = Ph, R' = C_6H_4-*o*-Cl), 84119-45-9; III(Ar = C_6H_4-*p*-Cl, R' = Me), 84119-46-0; III(Ar = C_6H_4-*p*-Cl, R' = Et), 84119-47-1; III(Ar = C_6H_4-*p*-Cl, R' = Bu), 84119-48-2; III(Ar = C_6H_4-*p*-Cl, R' = Ph), 84119-49-3; III(Ar = C_6H_4-*p*-Cl, R' = C_6H_4-*o*-Me), 84119-50-6; III(Ar = C_6H_4-*p*-Cl, R' = C_6H_4-*p*-Me), 84119-51-7; III(Ar = C_6H_4-*p*-Cl, R' = C_6H_4-*o*-OMe), 84119-52-8; III(Ar = C_6H_4-*p*-Cl, R' = C_6H_4-*o*-OEt), 84119-53-9; III(Ar = C_6H_4-*p*-Cl, R' = C_6H_4-*p*-OEt), 84119-54-0; III(Ar = C_6H_4-*p*-Cl, R' = C_6H_4-*o*-Cl), 84119-55-1; benzoyl isothiocyanate, 532-55-8; *S*-benzyl-*N*-phenylisothiourea, 28269-82-1; *S*-benzyl-*N*-(*p*-chlorophenyl)isothiourea, 39536-26-0; aniline, 62-53-3; *o*-methylaniline, 95-53-4; *m*-methylaniline, 108-44-1; *p*-methylaniline, 106-49-0; *o*-methoxyaniline, 90-04-0; *p*-methoxyaniline, 104-94-9; *p*-chloroaniline, 106-47-8; benzylamine, 100-46-9; butylamine, 109-73-9; methyl isothiocyanate, 556-61-6; ethyl isothiocyanate, 542-85-8; butyl isothiocyanate, 592-82-5; phenyl isothiocyanate, 103-72-0; *o*-methylphenyl isothiocyanate, 614-69-7; *p*-methylphenyl isothiocyanate, 622-59-3; *o*-methoxyphenyl isothiocyanate, 3288-04-8; *p*-methoxyphenyl isothiocyanate, 2284-20-0; *p*-ethoxyphenyl isothiocyanate, 3460-49-9; *o*-chlorophenyl isothiocyanate, 2740-81-0.

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Facile Synthesis of Benzimidazol-2-one Derivatives by Modified Lossen Rearrangement

Zygmunt Eckstein, Tadeusz Jadach,† and Ewa Lipczyńska-Kochany*

Institute of Organic Chemistry and Technology, Technical University of Warsaw, 00-662 Warsaw, Poland

A "formamide modification" has been applied to the Lossen rearrangement of several biologically important anthranilohydroxamic acids, some of them prepared for the first time. It has been found that a short heating at temperatures in the range 130–140 °C converts these compounds into corresponding benzimidazol-2-ones with excellent yields.

Unlike the Curtius and Hofmann rearrangements, the Lossen rearrangement (*1*) has not found wide applications in organic synthesis. The reason is that two preceding steps are usually essential to this reaction: an acylation of hydroxamic acid and then conversion to a salt, which can undergo rearrangement. In the past 20 years several modifications of the Lossen rearrangement have been reported, all of them attempts, more or less successful, to improve it (*2*, *3*). We should like to report the results of our recent attempt of an "amide modification" of this reaction as applied to the rearrangement of anthranilohydroxamic acids, known for their biological activities (*4*–*6*).

Results and Discussion

Eckstein noticed (*7*) that hydroxamic acids when heated in formamide underwent Lossen rearrangement without any previous treatment. On the basis of this observation we have examined the rearrangement of anthranilohydroxamic acids

† Graduate student.

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