

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

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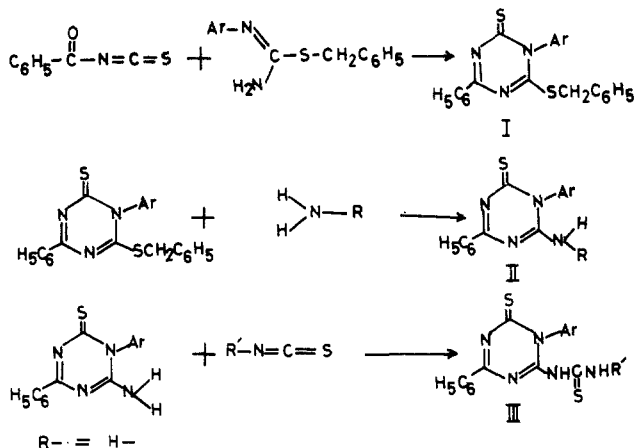
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Different

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-tri-



azinyl)-*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/anilino triazines (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 (CDCl₃) δ 4.525 (s, 2 H, CH₂), 7.208-7.881 (m, 15 H, ArH). By adoption of a similar procedure 2-(benzylmercapto)-1-(*p*-chlorophenyl)-4-phenyl-1,6-di-

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 ₆ H ₅	H	233	80
C ₆ H ₅	C ₆ H ₅	248	68
C ₆ H ₅	<i>o</i> -CH ₃ C ₆ H ₄	193	65
C ₆ H ₅	<i>m</i> -CH ₃ C ₆ H ₄	199	65
C ₆ H ₅	<i>p</i> -CH ₃ C ₆ H ₄	195	60
C ₆ H ₅	<i>o</i> -CH ₃ OC ₆ H ₄	176	55
C ₆ H ₅	<i>p</i> -CH ₃ OC ₆ H ₄	179	55
C ₆ H ₅	<i>p</i> -ClC ₆ H ₄	217	70
C ₆ H ₅	C ₆ H ₅ CH ₂	157	75
C ₆ H ₅	<i>n</i> -C ₄ H ₉	71	55
<i>p</i> -ClC ₆ H ₄	H	223	90
<i>p</i> -ClC ₆ H ₄	C ₆ H ₅	204	84
<i>p</i> -ClC ₆ H ₄	<i>m</i> -CH ₃ C ₆ H ₄	246	80
<i>p</i> -ClC ₆ H ₄	<i>p</i> -CH ₃ C ₆ H ₄	231	85
<i>p</i> -ClC ₆ H ₄	<i>o</i> -CH ₃ OC ₆ H ₄	196	65
<i>p</i> -ClC ₆ H ₄	<i>p</i> -CH ₃ OC ₆ H ₄	242	65
<i>p</i> -ClC ₆ H ₄	<i>m</i> -ClC ₆ H ₄	206	75
<i>p</i> -ClC ₆ H ₄	<i>p</i> -ClC ₆ H ₄	229	70
<i>p</i> -ClC ₆ H ₄	C ₆ H ₅ CH ₂	291	60
<i>p</i> -ClC ₆ H ₄	<i>n</i> -C ₄ H ₉	74	55

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

hydro-1,3,5-triazine-6-thione was prepared: yield 75%; mp 215 °C.

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 (CDCl₃) δ 3.80 (s, 1 H, NH), 7.316-7.85 (m, 15 H ArH). 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 (NH₂), 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

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

Ar	R'	mp, °C	yield, %
C ₆ H ₅	CH ₃	157	92
C ₆ H ₅	C ₂ H ₅	182	85
C ₆ H ₅	<i>n</i> -C ₄ H ₉	239	63
C ₆ H ₅	C ₆ H ₅	241	80
C ₆ H ₅	<i>o</i> -CH ₃ C ₆ H ₄	213	85
C ₆ H ₅	<i>p</i> -CH ₃ C ₆ H ₄	246	90
C ₆ H ₅	<i>o</i> -CH ₃ OC ₆ H ₄	219	80
C ₆ H ₅	<i>p</i> -CH ₃ OC ₆ H ₄	251	86
C ₆ H ₅	<i>p</i> -C ₂ H ₅ OC ₆ H ₄	197	65
C ₆ H ₅	<i>o</i> -ClC ₆ H ₄	224	88
<i>p</i> -ClC ₆ H ₄	CH ₃	162	95
<i>p</i> -ClC ₆ H ₄	C ₂ H ₅	229	85
<i>p</i> -ClC ₆ H ₄	<i>n</i> -C ₄ H ₉	239	75
<i>p</i> -ClC ₆ H ₄	C ₆ H ₅	234	85
<i>p</i> -ClC ₆ H ₄	<i>o</i> -CH ₃ C ₆ H ₄	237	80
<i>p</i> -ClC ₆ H ₄	<i>p</i> -CH ₃ C ₆ H ₄	232	84
<i>p</i> -ClC ₆ H ₄	<i>o</i> -CH ₃ OC ₆ H ₄	236	75
<i>p</i> -ClC ₆ H ₄	<i>o</i> -C ₂ H ₅ OC ₆ H ₄	243	65
<i>p</i> -ClC ₆ H ₄	<i>p</i> -C ₂ H ₅ OC ₆ H ₄	241	68
<i>p</i> -ClC ₆ H ₄	<i>o</i> -ClC ₆ H 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 = C₆H₄-*p*-Cl), 15998-34-2; II(Ar = Ph, R = H), 84119-18-6; II(Ar = R = Ph), 83490-26-0; II(Ar = Ph, R = C₆H₄-*o*-Me), 84119-19-7; II(Ar = Ph, R = C₆H₄-*m*-Me), 84119-20-0; II(Ar = Ph, R' = C₆H₄-*p*-Me), 84119-21-1; II(Ar = Ph, R = C₆H₄-*o*-OMe), 84119-22-2; II(Ar = Ph, R = C₆H₄-*p*-OMe), 84119-23-3; II(Ar = Ph, R = C₆H₄-*p*-Cl), 84119-24-4; II(Ar = Ph, R = CH₂-Ph), 84119-25-5; II(Ar = Ph, R = Bu), 84119-26-6; II(Ar = C₆H₄-*p*-Cl, R = H), 84119-27-7; II(Ar = C₆H₄-*p*-Cl, R = Ph), 84119-28-8; II(Ar = C₆H₄-*p*-Cl, R = C₆H₄-*m*-Me), 84119-29-9; II(Ar = C₆H₄-*p*-Cl, R = C₆H₄-*p*-Me), 84119-30-2; II(Ar = C₆H₄-*p*-Cl, R = C₆H₄-*o*-OMe), 84119-

31-3; II(Ar = C₆H₄-*p*-Cl, R = C₆H₄-*p*-OMe), 84119-32-4; II(Ar = C₆H₄-*p*-Cl, R = C₆H₄-*m*-Cl), 84119-33-5; II(Ar = R = C₆H₄-*p*-Cl), 84119-34-6; II(Ar = C₆H₄-*p*-Cl, R = CH₂-Ph), 84119-35-7; II(Ar = C₆H₄-*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' = C₆H₄-*o*-Me), 84119-41-5; III(Ar = Ph, R' = C₆H₄-*p*-Me), 84119-42-6; III(Ar = Ph, R' = C₆H₄-*o*-OMe), 84130-11-0; III(Ar = Ph, R' = C₆H₄-*p*-OMe), 84119-43-7; III(Ar = Ph, R' = C₆H₄-*p*-OEt), 84119-44-8; III(Ar = Ph, R' = C₆H₄-*o*-Cl), 84119-45-9; III(Ar = C₆H₄-*p*-Cl, R' = Me), 84119-46-0; III(Ar = C₆H₄-*p*-Cl, R' = Et), 84119-47-1; III(Ar = C₆H₄-*p*-Cl, R' = Bu), 84119-48-2; III(Ar = C₆H₄-*p*-Cl, R' = Ph), 84119-49-3; III(Ar = C₆H₄-*p*-Cl, R' = C₆H₄-*o*-Me), 84119-50-6; III(Ar = C₆H₄-*p*-Cl, R' = C₆H₄-*p*-Me), 84119-51-7; III(Ar = C₆H₄-*p*-Cl, R' = C₆H₄-*o*-OMe), 84119-52-8; III(Ar = C₆H₄-*p*-Cl, R' = C₆H₄-*o*-OEt), 84119-53-9; III(Ar = C₆H₄-*p*-Cl, R' = C₆H₄-*p*-OEt), 84119-54-0; III(Ar = C₆H₄-*p*-Cl, R' = C₆H₄-*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

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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

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