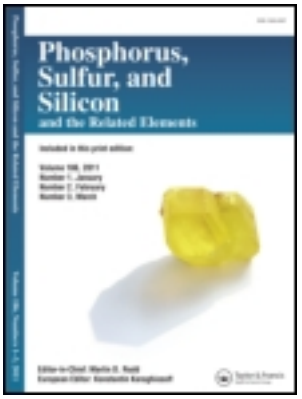

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Chemoselective Reaction of Benzoylisothiocyanates with Hydroxyl Group of Salicylamide: a New and Convenient Entry Into 2-Aryl-4H-benzo[e][1,3]oxazin-4-ones

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CHEMOSELECTIVE REACTION OF BENZOYLISOTHIOCYANATES WITH HYDROXYL GROUP OF SALICYLAMIDE: A NEW AND CONVENIENT ENTRY INTO 2-ARYL-4*H*-BENZO[E][1,3]OXAZIN-4-ONES

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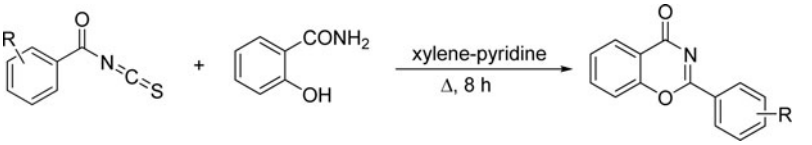
GRAPHICAL ABSTRACT



Abstract *The reactions of benzoylisothiocyanates with salicylamide in pyridine-xylene solution occurs chemoselectively at the hydroxyl group of the salicylamide to afford the corresponding O-benzoyl derivatives. The latter products, on prolonged heating in pyridine-xylene solution, undergo cyclodehydration to give 2-aryl-4H-benzo[e][1,3]oxazin-4-ones in good yields. These compounds could also be synthesized by a direct one-pot reaction of benzoylisothiocyanates with salicylamide by slow addition of benzoylisothiocyanates into a solution of salicylamide in xylene-pyridine solution under reflux. The products have been characterized on the basis of satisfactory analytical and spectral data.*

Keywords Benzoylisothiocyanates; salicylamide; bezoxazinones; cyclodehydration

INTRODUCTION

The reactions of heterocumulenes are of interest to organic chemists from a synthetic and mechanistic point of view. Our group is involved in the investigation of the reactivity of heterocumulenes, especially ketenes (C=C=O), with substrates having a nitrogen atom in different structural environments.[1] The reactions of ketenes often depend on the electronic environments of the nitrogen nucleophilic center in the molecule. For example, the reaction of diarylketenes with *N*-salicylideneamines containing two reactive sites, a hydroxyl group and an imine linkage, is observed to occur at the hydroxyl group in a chemoselective manner.[2] A similar reaction with benzophenone *N*-diphenylacyl hydrazones has been observed to take place at imino nitrogen but not at amidic nitrogen.[3] However, the reaction of

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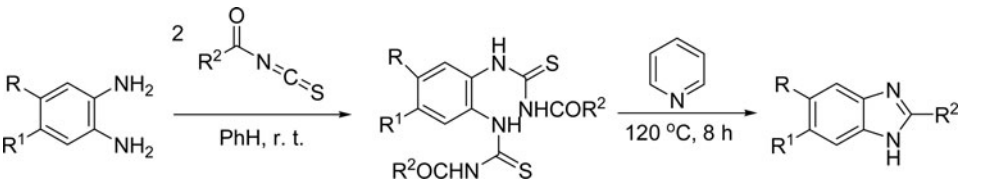
diphenylketene with 3-iminoisatins, which contain both amido nitrogen and imine linkage, occurs at amido nitrogen in the molecule.[4]

In continuation of these studies, we considered it pertinent to extend these investigations using heterocumulenes that contain C=N and C=S groups besides C=O such as benzoylisothiocyanates [ArC(O)N=C=S]. The latter compounds are easily accessible in the laboratory by reaction of the corresponding acyl chloride with ammonium thiocyanate. We envisioned that such isothiocyanates could show an even more interesting reactivity profile toward different nucleophiles that can be exploited for the synthesis of heterocyclic systems. A literature survey revealed that the reactions of benzoylisothiocyanates have drawn attention of organic chemists for applications in organic synthesis and medicinal chemistry.[5] It has been observed that the reactivity of such isothiocyanates often depends on structure of isothiocyanates besides the other substrate in the reaction, solvents, and reaction conditions.[6] Recently, the reaction of benzoylisothiocyanate with 2-aminobenzothiophenes has been employed in the synthesis of annulated thiophene derivatives.[7] Our group recently carried out the reactions of differently substituted benzoylisothiocyanates with symmetrical bis-nucleophiles 1,2-phenylenediamines forming 2-arylbenzimidazoles.[8] The usual bis-thiourea products were cyclized by refluxing in pyridine to afford the 2-arylbenzimidazoles (Scheme 1). In the present paper, we wish to report the reactions of benzoylisothiocyanates with an unsymmetrical bis-nucleophile salicylamide leading to the formation of 2-aryl-4*H*-benzo[e][1,3]oxazin-4-ones. The reaction of benzoylisothiocyanates occurs chemoselectively at the hydroxyl group of salicylamide affording 2-(*O*-benzoyl)benzamides. The latter compounds cyclize on prolonged heating to afford the 2-aryl-4*H*-benzo[e][1,3]oxazin-4-ones.



Scheme 1

Benzoxazinones constitute an important class of heterocyclic compounds and have been extensively explored as pharmaceuticals and agrochemicals.[9] A few earlier studies on the synthesis of 2-aryl-4*H*-benzo[e][1,3]oxazin-4-ones using salicylamide involve its reaction with carbonyl compounds such as acid chlorides and ethyl chloroformate.[10,11,12] A reaction of 1-aryl-1-chloro-2,2,2-trifluoromethylisocyanate with phenols is reported to yield 2-aryl-2-trifluoromethyl-2,3-dihydro-4*H*-benzo[e][1,3]oxazin-4-ones via cyclization of an iminoester intermediate.[13] This paper is, to the best of our knowledge, the first entry to a benzoxazinone system employing a sulfur-containing reagent.

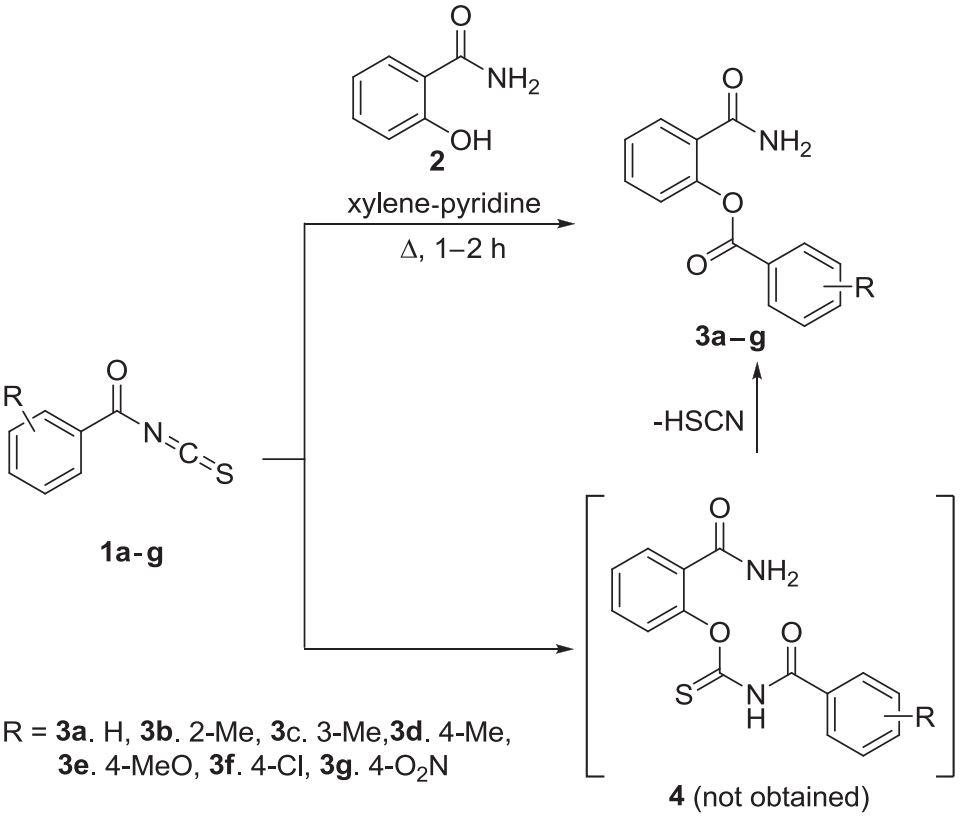
RESULTS AND DISCUSSION

An equimolar reaction of benzoylisothiocyanate **1a** with salicylamide **2** by refluxing in xylene-pyridine (5:1) for 1 h afforded a white crystalline product. This product was characterized as *O*-benzoyl derivative **3a** of salicylamide on the basis of satisfactory analytical and spectral data discussed briefly in the succeeding paragraph. The use of a base,

pyridine in this case, was a necessity for the reaction of isothiocyanates with a phenolic hydroxyl group.[14] The xylene-pyridine ratio was optimized by carrying out the reaction in three different ratios of xylene-pyridine (5:0.5, 5:1, and 5:2). The maximum yield could be obtained in minimum time using the xylene-pyridine ratio of 5:1.

The IR spectrum of the product **3a** showed strong absorption bands at 1717 cm^{-1} and 1670 cm^{-1} corresponding to ester and amide carbonyls, respectively. The ^1H NMR spectra showed signals corresponding to nine aromatic protons besides a D_2O-exchangeable downfield signal at $\delta = 10.34$ ppm accounting for two amido nitrogen protons.

A similar reaction of salicylamide with differently substituted benzoylisothiocyanates **1b–g** afforded the corresponding *O*-benzoyl derivatives **3b–g** (Scheme 2), identified on the basis of their analytical and spectral data (see Experimental). The reactions of 4-chloro- and 4-nitrobenzoylisothiocyanates **1f**,**g** containing electron-withdrawing groups required more time (2 h) in comparison with other isothiocyanates. Anticipated adducts **4** could not be isolated in any case because of an easy elimination of thiocyanic acid in pyridine.

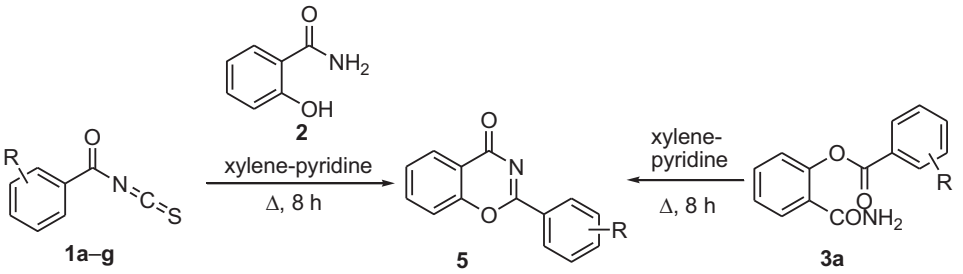


Scheme 2

The formation of only one product in these reactions clearly demonstrates the higher reactivity of isothiocyanates toward the hydroxyl group. It is worth mentioning here that the chemoselective reactions are of immense importance for the synthetic organic chemists to avoid unnecessary protection and deprotection steps, and also to reduce the cost of overall

synthetic processes. The reaction of a particular functional group, selectively, in complex molecules containing more than one functional group is a challenging endeavor in organic chemistry.

With seven *O*-aroyl derivatives of salicylamide in hand, it was considered useful to extend the scope of the reaction for the synthesis of heterocyclic compounds. With this objective, the pyridine solution of compound **3a** was added slowly over 6 h in refluxing xylene. The reaction mixture was refluxed for an additional 2 h. It resulted into cyclodehydration of **3a** to afford the crystalline product characterized as 2-aryl-4*H*-benzo[e][1,3]oxazin-4-one **5a** (Scheme 3) on the basis of satisfactory analytical and spectral data and by comparison with an authentic sample. The observation that cyclodehydration of **3a** took place easily affording the heterocyclic system prompted us to develop a one-pot method for synthesis of compounds **5a–g** from the reaction of salicylamide **2** with benzoylisothiocyanates **1a–g**. A slow addition (6 h) of the appropriate benzoylisothiocyanate to salicylamide **2** in xylene-pyridine solution followed by an additional reflux for 2 h afforded products **5a–g** (Scheme 3) in good yields (see Experimental). This direct synthesis of benzoxazinones, however, was unsuccessful in either xylene or pyridine alone.



R = **5a**. H, **5b**. 2-Me, **5c**. 3-Me, **5d**. 4-Me, **5e**. 4-MeO, **5f**. 4-Cl, **5g**. 4-O_2N

Scheme 3

CONCLUSION

The study reports a chemoselective reaction of benzoylisothiocyanates with the hydroxyl group of the salicylamide forming the corresponding 2-(*O*-aroyl)benzamides. This finding led us to develop a new and convenient one-pot method for the synthesis of 2-aryl-4*H*-benzo[e][1,3]oxazin-4-ones through the cyclodehydration of 2-(*O*-aroyl)benzamides in pyridine-xylene solution. An easy work-up and relatively good yields of the products make this method a useful addition to the arsenal of synthetic methods for such compounds.

EXPERIMENTAL

Melting points have been recorded on a Gallenkamp melting point apparatus and are uncorrected. The IR spectra were recorded on a Jasco FT-IR 5300 IR spectrophotometer using nujol mull of the sample. The ^{1}H NMR spectra were recorded in a DMSO-d_6 solution at 90 MHz on a Jeol FX-90Q 90 MHz spectrometer. The elemental analyses have been carried out on a Perkin–Elmer CHN Analyzer 240 C. Salicylamide was procured from the

Aldrich Chemicals, and benzoylisothiocynates were prepared by reactions of acid chlorides with potassium thiocyante according to the reported methods.[15]

General Procedure for the Preparation of 2-(*O*-aroyl)Benzamides 3a–g

An appropriate benzoylisothiocyanate (10 mmol) was added to a solution of salicylamide (10 mmol) in xylene (10.0 mL) and pyridine (2.0 mL). The reaction mixture was refluxed for 1–2 h and the progress of reaction was monitored by thin layer chromatography (TLC). After the completion of the reaction, the reaction flask was allowed to cool to room temperature. The solid product that appeared in the flask was filtered and recrystallized with ethanol.

Compound 3a: White crystalline solid; yield: 86%; mp 143–144 °C (lit mp 143–144 °C)[16]; IR (Nujol, ν cm^{-1}): 3400, 3200, 1717, 1670, 1600, 1518, 1481; ^{1}H NMR (DMSO-d$_6$, 90 MHz) δ: 7.51 (9H, Ar$_H$), 10.34 (bs, 2H, CONH_2); found: C 69.42, H 4.74, N 5.60% (calculated for $C_{14}H_{11}NO_3$: C 69.70, H 4.60, N 5.81%).

Compound 3b: White crystalline solid; yield: 74%; mp 201–202 °C; IR (Nujol, ν cm^{-1}): 3420, 3246, 1720, 16780, 1590, 1500, 1465; ^{1}H NMR (DMSO-d$_6$, 90 MHz) δ: 2.64 (s, 3H, CH_3), 7.65 (8H, Ar$_H$), 10.09 (bs, 2H, CONH_2); found: C 70.25, H 5.37, N 5.36% (calculated for $C_{15}H_{13}NO_3$: C 70.58, H 5.13, N 5.49%).

Compound 3c: White crystalline solid; yield: 79%; mp 210–212 °C; IR (Nujol, ν cm^{-1}): 3410, 3240, 1715, 1675, 1590, 1520, 1470; ^{1}H NMR (DMSO-d$_6$, 90 MHz) δ: 2.41 (s, 3H, CH_3), 7.62 (8H, Ar$_H$), 10.42 (bs, 2H, CONH_2); found: C 70.20, H 5.45, N 5.38% (calculated for $C_{15}H_{13}NO_3$: C 70.58, H 5.13, N 5.49%).

Compound 3d: White crystalline solid; yield: 83%; mp 240–241 °C; IR (Nujol, ν cm^{-1}): 3420, 3250, 1717, 1680, 1600, 1480; ^{1}H NMR (DMSO-d$_6$, 90 MHz) δ: 2.22 (s, 3H, CH_3), 7.64 (8H, Ar$_H$), 10.41 (bs, 2H, CONH_2); found: C 70.33, H 5.32, N 5.25% (calculated for $C_{15}H_{13}NO_3$: C 70.58, H 5.13, N 5.49%).

Compound 3e: White crystalline solid; yield: 80%; mp 166–167 °C (lit mp 166–167 °C)[16]; IR (Nujol, ν cm^{-1}): 3420, 3250, 1720, 1680, 1590, 1520, 1454; ^{1}H NMR (DMSO-d$_6$, 90 MHz) δ: 3.91 (s, 3H, OCH_3), 7.52 (8H, Ar$_H$), 10.51 (bs, 2H, CONH_2); found: C 66.00, H 5.12, N 4.89% (calculated for $C_{15}H_{13}NO_4$: C 66.41, H 4.83, N 5.16%).

Compound 3f: White crystalline solid; yield: 75%; mp 225–227 °C (lit mp 225–227 °C)[16]; IR (Nujol, ν cm^{-1}): 3425, 3240, 1715, 1680, 1580, 1550, 1500; ^{1}H NMR (DMSO-d$_6$, 90 MHz) δ: 7.58 (8H, Ar$_H$), 10.42 (bs, 2H, CONH_2); found: C 60.65, H 3.90, N 5.12% (calculated for $C_{14}H_{10}NO_3Cl$: C 60.99, H 3.66, N 5.08%).

Compound 3g: Light yellow crystals; yield: 73%; mp 212–214 °C (lit mp 212–214 °C)[16]; IR (Nujol, ν cm^{-1}): 3420, 3235, 1715, 1675, 1610, 1580, 1550; ^{1}H NMR (DMSO-d$_6$, 90 MHz) δ: 7.56 (8H, Ar$_H$), 10.28 (bs, 2H, CONH_2); found: C 58.30, H 3.78, N 9.50% (calculated for $C_{14}H_{10}N_2O_5$: C 58.74, H 3.52, N 9.79%).

General Procedures for the Synthesis of Oxazin-4-Ones 5a–g

By cyclodehydration of 2-(O-aroyl)benzamides **3a**: A solution of appropriate 2-(*O*-aroyl)benzamides (5 mmol) in pyridine (5.0 mL) was added drop-wise over 6 h to refluxing xylene (15.0 mL) in an oil bath at 145 °C. The solution was refluxed for an additional 2 h. Removal of pyridine and xylene under reduced pressure afforded a solid product that was washed with water, dried, and recrystallized with ethanol.

Compound 5a: Brown solid; yield: 60%; mp 102–103 °C; IR (Nujol, ν cm^{-1}): 1755, 1660, 1600, 1450; ^{1}H NMR (DMSO-d$_6$, 90 MHz) δ: 7.54 (9H, Ar$_H$), found: C 74.95, H 4.35, N 6.00% (calculated for $C_{14}H_9NO_2$: C 75.33, H 4.06, N 6.27%).

By one-pot reaction of benzoylisothiocyanates **1a–g** *with salicylamide* **2**: An appropriate benzoylisothiocynate (10 mmol) was added drop-wise during 8 h to a refluxing solution of salicylamide (10 mmol) in xylene (10.0 mL) and pyridine (2.0 mL) in an oil bath at 145 °C. Pyridine (2.0 mL) was added again and refluxing was continued for additional 2 h. Removal of pyridine and xylene under reduced pressure afforded a solid product that was washed with water, dried, and recrystallized with ethanol.

Compound 5a: Brown solid; yield: 55%; mp 102–103 °C (undepressed mixed melting point with the compound **5a** prepared by cyclodehydration of 2-(*O*-aroyl)benzamides **3a**).

Compound 5b: Reddish brown solid; yield: 57%; mp 178–180 °C; IR (Nujol, ν cm^{-1}): 1740, 1650, 1590, 1470; ^{1}H NMR (DMSO-d$_6$, 90 MHz) δ: 2.82 (s, 3H, CH_3), 7.56 (8H, Ar$_H$), found: C 76.22, H 4.52, N 5.82% (calculated for $C_{15}H_{11}NO_2$: C 75.93, H 4.67, N 5.90%).

Compound 5c: White solid; yield: 60%; mp 170–171 °C; IR (Nujol, ν cm^{-1}): 1760, 1650, 1590, 1460; ^{1}H NMR (DMSO-d$_6$, 90 MHz) δ: 2.63 (s, 3H, CH_3), 7.55 (8H, Ar$_H$), found: C 75.74, H 4.38, N 5.81% (calculated for $C_{15}H_{11}NO_2$: C 75.93, H 4.67, N 5.90%).

Compound 5d: White solid; yield: 65%; mp 201–203 °C; IR (Nujol, ν cm^{-1}): 1760, 1650, 1590, 1460; ^{1}H NMR (DMSO-d$_6$, 90 MHz) δ: 2.42 (s, 3H, CH_3), 7.47 (8H, Ar$_H$), found: C 75.66, H 4.53, N 6.12% (calculated for $C_{15}H_{11}NO_2$: C 75.93, H 4.67, N 5.90%).

Compound 5e: White solid; yield: 67%; mp 185–186 °C (lit. mp 184–186 °C);[16] IR (Nujol, ν cm^{-1}): 1755, 1670, 1590, 1465; ^{1}H NMR (DMSO-d$_6$, 90 MHz) δ: 3.84 (s, 3H, OCH_3), 7.54 (8H, Ar$_H$), found: C 70.82, H 4.60, N 5.60% (calculated for $C_{15}H_{11}NO_3$: C 71.14, H 4.38, N 5.53%).

Compound 5f: White solid; yield: 60%; mp 171–172 °C (lit. mp 172 °C);[16]IR (Nujol, ν cm^{-1}): 1730, 1650, 1600, 1500; ^{1}H NMR (DMSO-d$_6$, 90 MHz) δ: 7.48 (8H, Ar$_H$), found: C 64.95, H 3.38, N 5.66% (calculated for $C_{14}H_8NO_2Cl$: C 65.26, H 3.13, N 5.44%).

Compound 5g: Red needles; yield: 55%; mp 192–194 °C; IR (Nujol, ν cm^{-1}): 1750, 1650, 1590, 1520; ^{1}H NMR (DMSO-d$_6$, 90 MHz) δ: 7.56 (8H, Ar$_H$), found: C 62.35, H 3.30, N 10.65% (calculated for $C_{14}H_8N_2O_4$: C 62.68, H 3.00, N 10.44%).

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