# Imidoyl isothiocyanates in the synthesis of condensed heterocycles: preparation of some substituted benzotriazocines

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**Dedicated to Professor Ľubor Fišera on his 60th anniversary**
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**Abstract**
By modification of the known literature procedures, the key intermediate product – *N*-phenyl(phenylimino)methylchloromethanimidoyl chloride **3** was prepared. Nucleophilic substitution reactions of the prepared imidoyl chloride with various secondary amines gave the corresponding intermediates, very useful for the syntheses of corresponding imidoyl isothiocyanates **5a-e**. The subsequent cyclization reaction of these isothiocyanates afforded novel substituted 1,3,5-benzotriazocine derivatives **6a-e** .

**Keywords:** Imidoyl chlorides, imidoyl dichlorides, imidoyl isothiocyanates, benzotriazocine-thiones

## Introduction

As homologues of quinazoline, heterocyclic compounds such as 1,4-benzodiazepines and 1,5-benzodiazocines, can be expected to display a number of similar properties. The presence of a larger heterocyclic ring engenders changes in the spatial arrangement and hence also the manifestation of different properties. The best way to visualize these differences is to compare the respective bioactivities. While quinazolines have been known to possess a wide scope of pharmacological properties in addition to being phyto-effective, benzodiazepines and benzodiazocines are better known as central nervous system agents.

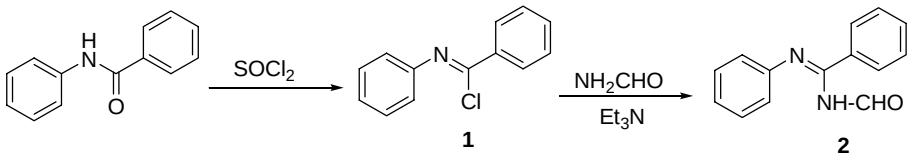
These findings have stimulated our efforts to synthesize novel bioactive benzodiazocines.

The synthetic approach to the majority of benzodiazocines, azepines and azocines starts from anilines carrying a carbonyl group in the 2 position. Such a bifunctional substrate can serve as starting material for building up further rings, utilizing the available amino- or carbonyl group, and leading ultimately to fused 6-, 7-, or 8-membered rings.

For the preparation of 8-membered benzoannelated steps we selected the easily available [(4-chlorophenyl)(phenylimino)methyl]carbonimidic dichloride **3,** a starting material prone to further nucleophilic substitutions, and suitable for preparation of target heterocyclic rings.

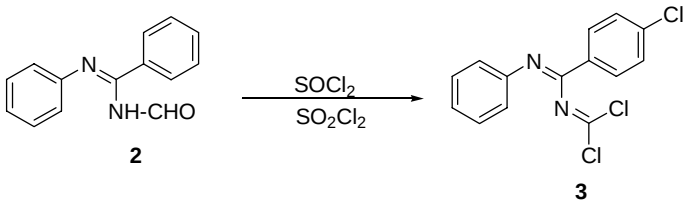
## Results and Discussion

*N*-Phenylbenzenecarboximidoyl chloride **1,** treated with formamide in the presence of triethylamine, gave rise to the intermediate *N*-formyl-*N′*-phenylbenzenecarboximidamide **2**,




**Scheme 1.** Synthesis of *N*-formyl-*N′*-phenylbenzenecarboximidamide.

Radical chlorination of the *N*-formyl-*N′*-phenylbenzenecarboximidamide **2** afforded the key intermediate - [(4-chlorophenyl)(phenylimino)methyl]carbonimidic dichloride **3.** The **c**hlorination was carried out as a one-pot process, using sulfuryl chloride dissolved in thionyl chloride. In addition to serving as solvent, thionyl chloride had also a dehydrating effect. Under the above reaction conditions however, radical chlorination took not only place at the expected formamide carbon, but at one aromatic ring as well. Our observation and the structure of the isolated product was confirmed by $^{13}C$ and $^{1}H$ NMR spectra. Since the target dichloride **3** decomposes rapidly, it appeared more convenient for synthetic purposes to use it directly without purification. The quality of the crude product proved sufficient for the subsequent reaction.

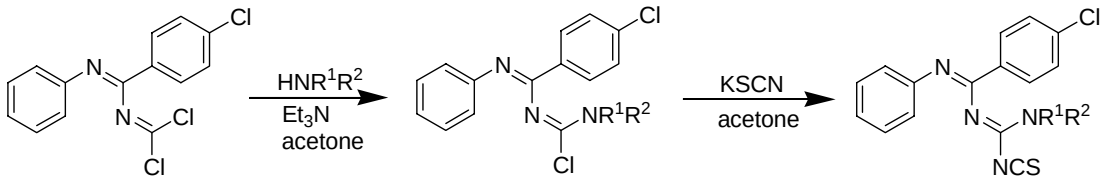



**Scheme 2.** Chlorination of *N*-formyl-*N′*-phenylbenzenecarboximidamide.

Numerous reactions of carboimidoyl dichlorides with nucleophiles, such as secondary amines, alcoholates, phenolates and thiols[5], have been published. Using the propensity of carboimidoyl dichlorides to nucleophilic substitutions, we modified [(4-chlorophenyl)(phenylimino)methyl]carbonimidic dichloride **3** by reactions with various secondary amines to the corresponding *N*-[(4-chlorophenyl)(phenylimino)methyl]-R-4-

carboximidoyl chlorides **4a-e.** The latter are usually prepared in inert solvents (benzene, toluene) in the presence of a base. In our hands the best results were achieved in anhydrous acetone with triethylamine as base. Using anhydrous acetone allowed us to filter off the triethylamine hydrochloride after completion of the reaction and use the acetone solution of substituted carboximidoyl chloride directly in the following reaction with potassium thiocyanate.

For analytical measurements the acetone solutions of **4a-e** were, after filtering off the triethylamine hydrochloride, concentrated *in vacuo* and the crude product was purified by crystallization from acetonitrile.

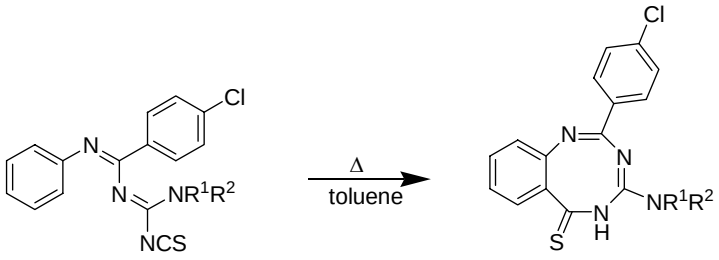



**3** **4a-e** **5a-e**

R = $HNR^1R^2$: **a**=Morpholine, **b**=Piperidine, **c**=*N*-methylpiperazine**, d**=*N*-phenylpiperazine, **e**=*N*-ethylaniline

**Scheme 3.** Preparation of substituted carboximidoyl isothiocyanates **5a-e**.

The last synthetic step involved a thermal intramolecular cyclization in boiling toluene of the freshly prepared *N´´´*-[(4-chlorophenyl) (phenylimino)methyl]-R-carboximidoyl isothiocyanates **5a-e**. After completion of the reaction, isolation and purification of the product, the desired 2-(4-chlorophenyl)-4-R-1,3,5-benzotriazocine-6(*5H*)-thiones **6a-e** were obtained.




**5a-e** **6a-e**

**Scheme 4.** Thermal cyclization of *N´´´*-[(4-chlorophenyl)(phenylimino)methyl]-R-carboximidoyl isothiocyanates.

In conclusion, we have developed an efficient, mild and spontaneous method for synthesis of the rare 1,3,5-benzotriazocines, and provided further examples of the utility of imidoyl isothiocyanates in organic syntheses of benzazocines and their analogues.

## Experimental Section

**General Procedures.** Melting points were determined using a Kofler hot-stage apparatus and are uncorrected. IR spectra of compounds in KBr pellets were measured with a Philips PV 9800 FTIR apparatus.

$^{1}H$ and $^{13}C$ NMR spectra were recorded on a Varian VXR 300 spectrometer in $(CD_3)_2SO$ and tetramethylsilane was used as an internal standard.

Preparation on starting *N*-phenylbenzenecarboximidoyl chloride **1** was reported in Ref[6].

***N*-formyl-*N′*-phenylbenzenecarboximidamide (2).** To a solution of *N*-phenylbenzene carboximidoyl chloride in dry benzene (125mL) triethylamine (16 mL, 0.12 mol) and formamide (3.8 mL, 0.12 mol) were added. The reaction mixture was refluxed for 1 h. After cooling, the formed precipitate was filtered off, washed with hot water and crystallized from toluene.

White plates; Yield (18 g, 67%). mp 171-173°C. IR (KBr): 3343, 3051, 1655 $cm^{-1}$. $^{1}H$ NMR ($CDCl_3$): δ 7.13-7.93 (m, 10H-arom.). Anal. Calcd. for $C_{14}H_{12}N_2O$ (224.26): C, 74.98; H, 5.39; N, 12.49. Found: C, 74.54; H, 5.09; N, 12.13.

**[(4-Chlorophenyl)(phenylimino)methyl]carbonimidic dichloride (3).** To the mixture of thionyl chloride (100 mL) and sulphuryl chloride (10.9 mL, 0.134 mol) *N*-formyl-*N′*-phenylbenzene carboximidamide **2** (30 g, 0.134 mol) was added. The reaction mixture was stirred at room temperature for 24 h, and was heated up to 80°C. Excess of thionyl chloride was removed and the crude product was recrystallized from *n*-hexane.

White needles; Yield (22 g, 53 %), mp 60-63°C. $^{1}H$ NMR ($CDCl_3$) δ 6.94-8.16 (m, 9H-arom). $^{13}C$ NMR ($CDCl_3$) δ 121.9, 128.5, 129.0, 129.4, 130.5, 132.2, 135.2, 144.1, 146.1. Anal. Calcd. for $C_{14}H_9Cl_3N_2$ (311.6): C, 53.96; H, 2.91; N, 8.99. Found: C, 53.63; H, 2.55; N, 8.31.

**General procedure for the preparation of *N*-[(*Z*)-(4-chlorophenyl)(phenylimino)methyl]-*R*-carboximidoyl chloride 4a-e**

To the solution of [(4-chlorophenyl)(phenylimino) methyl]carbonimidic dichloride **3** (2 g, 0.0055 mol) in dry acetone (10 mL) the equimolar amount of triethylamine (0.78 mL, 0.0055 mol) was added. The solution was cooled to 0°C, and the secondary amine (0.0055 mol) was added dropwise. The reaction mixture was stirred at room temperature for 2 h. The precipitated triethylamine hydrochloride was filtered off, the solvent was removed by distillation and the crude product was crystallized from acetonitrile.

***N*-[(4-Chlorophenyl)(phenylimino)methyl]morpholine-4-carboximidoyl chloride (4a).** Beige crystals (91%), mp 100-103°C. $^{1}H$ NMR ($CDCl_3$) δ 6.46-7.52 (m, 9H-arom), 3.43-3.79 (m, 9H-morpholine); Anal. Calcd. for $C_{18}H_{17}Cl_2N_3O$ (362.25): C, 59.68; H, 4.73; N, 11.60. Found: C, 59.40; H, 4.70; N, 11.42.

***N*-[(4-Chlorophenyl)(phenylimino)methyl]piperidine-1-carboximidoyl chloride (4b).** Dark oil( 95%). $^{1}H$ NMR ($CDCl_3$) δ 6.43-8.20 (m, 9H-arom), 3.40 (m, 4H-piperidine), 1.63 (m, 6H-

piperidine); Anal. Calcd. for $C_{19}H_{19}Cl_2N_3$ (360.27): C, 63.34; H, 5.32; N, 11.66. Found: C, 63.15; H, 5.25; N, 11.43.

***N*-[(4-Chlorophenyl)(phenylimino)methyl]-4-methylpiperazine-1-carboximidoyl chloride (4c).** Dark yellow oil (95%), $^1$H NMR ($CDCl_3$) δ 6.41-7.53 (m, 9H-arom), 3.45-3.56 (m, 4H-*N*-methylpiperazine), 2.46-2.61 (m, 4H-*N*-methylpiperazine), 2.39 (s, 3H, $CH_3$). Anal. Calcd. for $C_{19}H_{20}Cl_2N_4$ (375.29): C, 60.80; H, 5.37; N, 14.93. Found: C, 60.55; H, 5.30; N, 14.69.

***N*-[(4-Chlorophenyl)(phenylimino)methyl]-4-phenylpiperazine-1-carboximidoyl chloride (4d).** Yelllow crystals (71%), mp 180-183°C. $^1$H NMR ($CDCl_3$) δ 6.55-8.12 (m, 14H-arom), 3.20-3.70 (m, 8H-*N*-phenylpiperazine). Anal. Calcd. for $C_{24}H_{22}Cl_2N_4$ (437.36): C, 65.90; H, 5.07; N, 12.81. Found: C, 65.70; H, 4.99; N, 12.56.

***N*'-[(4-Chlorophenyl)(phenylimino)methyl]-*N*-ethyl-*N*-phenylcarbamimidic chloride (4e).** Brown oil (95%), $^1$H NMR ($CDCl_3$) δ 6.73-7.15 (m, 14H-arom), 4.30 (q, 2H, $\underline{CH_2}CH_3$), 1.25 (t, 3H, $CH_2\underline{CH_3}$). Anal. Calcd. for $C_{22}H_{19}Cl_2N_3$ (396.30): C, 66.67; H, 4.83; N, 10.60. Found: C, 66.40; H, 4.73; N, 10.31.

**General procedure for the preparation of *N´´´*-[(4-chlorophenyl)(phenylimino)methyl]-R-carboximidoyl isothiocyanates 5a-e**

To the acetone solution of the corresponding carboximidoyl chloride (0.0055 mol) cooled to -10°C, potassium thiocyanate (0.5 g, 0.0055 mol) in dry acetone (10 mL) was added dropwise. The reaction mixture was stirred at 0°C for 1 h. Precipitated KCl was filtered off, the solvent was removed under vacuum and the crude product was used in the next reaction without purification.

***N*'''-[(4-Chlorophenyl)(phenylimino)methyl]morpholine-4-carboximidoyl isothiocyanate (5a).** Beige crystals (94%), mp 103-105°C. IR (KBr): 2048, 1626, 1585 cm$^{-1}$. Anal. Calcd. for $C_{18}H_{17}Cl_2N_3O$ (362.25): C, 59.29; H, 4.45; N, 14.46. Found: C, 59.11; H, 4.40; N, 14.41.

***N*'''-[(4-chlorophenyl)(phenylimino)methyl]piperidine-1-carboximidoyl isothiocyanate (5b).** Oil (73%), IR (KBr): 2081, 1583 cm$^{-1}$. Anal. Calcd. for $C_{20}H_{19}ClN_4S$ (382.90): C, 62.73; H, 5.00; N, 14.63. Found: C, 62.53; H, 4.95; N, 14.35.

***N*'''-[(4-Chlorophenyl)(phenylimino)methyl]-4-methylpiperazine-1-carboximidoyl isothiocyanate (5c).** Yellow crystals (58%), mp 91-93°C. IR (KBr): 2050, 1613, 1597, 1587 cm$^{-1}$. Anal. Calcd. for $C_{20}H_{20}ClN_5S$ (397.92): C, 60.32; H, 5.07; N, 17.60. Found: C, 60.19; H, 5.00; N, 17.45.

***N*'''-[(4-Chlorophenyl)(phenylimino)methyl]-4-phenylpiperazine-1-carboximidoyl isothiocyanate (5d).** Oak crystals (71%), mp 195-198°C. IR (KBr): 2056, 1647, 1594 cm$^{-1}$. Anal. Calcd. for $C_{25}H_{22}ClN_5S$ (459.99): C, 65.27; H, 4.82; N, 15.23. Found: C, 65.01; H, 4.72; N, 15.04.

***N*''''-[4-Chlorophenyl)(phenylimino)methyl]-*N*-ethyl-*N*-phenylcarbamimidic isothiocyanate (5e).** Beige crystals ( 70%), mp 98-100°C. IR (KBr): 2060, 1651, 1595 cm$^{-1}$. Anal. Calcd. for $C_{223}H_{19}ClN_4S$ (418.93): C, 65.94; H, 4.57; N, 13.37. Found: C, 65.75; H, 4.48; N, 13.10.

**General procedure for the preparation of 2-(4-chlorophenyl)-4-X-1,3,5-benzotriazocine-6(5*H*)-thiones 6a-e**

The corresponding carboximidoyl isothiocyanate (0.004 mol) in dry toluene (25 mL) was refluxed for 8 h. The solvent was removed under vacuum and the resultant crude product was crystallised from acetonitrile.

**2-(4-Chlorophenyl)-4-morpholin-4-yl-1,3,5-benzotriazocine-6(5*H*)-thione (6a).** White needles (67%), mp 116-118°C. $^1$H NMR ($CDCl_3$) δ 6.49-7.28 (m, 8H-arom), 3.43-3.74 (m, 8H-morpholine). $^{13}$C NMR ($CDCl_3$) δ 46.69, 46.78, 46.84, 46.90, 66.71 (4C-morpholine); 124.12, 126.75, 128.25, 128.54, 129.00, 129.23, 132.23 (12C-arom.); 148.48 (1C, C=N); 161.14 (1C, C=S). Anal. Calcd. for $C_{19}H_{17}ClN_4OS$ (384.88): C, 59.29; H, 4.45; N, 14.56. Found: C, 59.20; H, 4.41; N, 14.51.

**2-(4-Chlorophenyl)-4-piperidin-1-yl-1,3,5-benzotriazocine-6(5*H*)-thione (6b).** Yellow crystals (63%), mp 94-96°C. $^1$H NMR ($CDCl_3$) δ 6.45-7.24 (m, 8H-arom), 3.35-3.38 (m, 4H-piperidine), 1.66-1.60(m, 4H-piperidine). $^{13}$C NMR ($CDCl_3$) δ 24.84, 25.85, 47.00 (5C-piperidine); 122.55, 124.18, 125.78, 128.05, 128.24, 128.61, 128.74, 128.86, 129.15, 130.91, 132.39, 133.66 (12C-arom.); 146.72, 150.03 (2C, C=N); 161.01 (1C, C=S). Anal. Calcd. for $C_{20}H_{19}ClN_4S$ (382.90): C, 62.73; H, 5.00; N, 14.63. Found: C, 62.68; H, 4.98; N, 14.55.

**2-(4-Chlorophenyl)-4-(4-methylpiperazin-1-yl)-1,3,5-benzotriazocine-6(5*H*)-thione (6c).** Cream-coloured crystals (28%), mp 147-149°C. $^1$H NMR ($CDCl_3$) δ 6.73-7.95 (m, 8H-arom), 3.77 (m, 4H-*N*-methylpiperazine), 2.96 (m, 4H-*N*-methylpiperazine), 2.61 (s, 3H, $CH_3$). $^{13}$C NMR ($CDCl_3$) δ 44.28 (1C, $CH_3$); 45.76, 53.58 (4C-*N*-methylpiperazine); 125.16, 127.36, 128.76, 128.83, 129.22, 129.29, 129.40, 129.45, 129.60, 131.04, 134.70, 136.80 (12C-arom.); 143.30, 149.60 (2C, C=N); 161.61 (1C, C=S). Anal. Calcd. for $C_{20}H_{20}ClN_5S$ (397.92): C, 60.36; H, 5.07; N, 17.60. Found: C, 60.30; H, 5.00; N, 17.52.

**2-(4-Chlorophenyl)-4-(4-phenylpiperazin-1-yl)-1,3,5-benzotriazocine-6(5*H*)-thione (6d).** Beige needles (30%), mp 218-220°C. $^1$H NMR ($CDCl_3$) δ 6.47-7.31 (m, 13H-arom), 3.57 (m, 4H-*N*-phenylpiperazine), 3.21(m, 4H-*N*-phenylpiperazine). $^{13}$C NMR ($CDCl_3$) δ 45.85, 45.90, 45.97, 46.04, 49.30 (4C-*N*-phenylpiperazine); 116.43, 120.23, 121.40, 123.98, 126.26, 127.00, 128.17, 128.43, 128.83, 128.97, 129.09, 129.19, 132.02, 132.93 (18C-arom.); 149.51, 151.17 (2C, C=N); 160.74 (1C, C=S).Anal. Calcd. for $C_{25}H_{22}ClN_5S$ (459.99): C, 65.27; H, 4.82; N, 15.23. Found: C, 65.15; H, 4.73; N, 15.09.

**2-(4-Chlorophenyl)-4-[ethyl(phenyl)amino]-1,3,5-benzotriazocine-6(5*H*)-thione (6e).** Light yellow crystals (25%), mp 106-107°C. $^1$H NMR ($CDCl_3$) δ 6.45-7.25 (m, 13H-arom), 4.06 (q, 2H, $\underline{CH_2}CH_3$), 1.39 (t, 3H, $CH_2\underline{CH_3}$). $^{13}$C NMR ($CDCl_3$) δ 12.61, 46.43 (2C-ethyl); 123.95, 125.24, 126.28, 127.61, 127.93, 128.17, 128.60, 130.09, 130.72, 133.57 (18C-arom.); 144.46, 149.73 (2C, C=N); 158.86 (1C, C=S). Anal. Calcd. for $C_{23}H_{19}ClN_4S$ (418.93): C, 65.94; H, 4.57; N, 13.37. Found: C, 65.83; H, 4.45; N, 13.20.

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