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3-Aryl/hetaryl-2-cyanoacryloyl chlorides: Synthesis and Reactions with Binucleophiles Targeting Heterocycles

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Abstract

In this review, we reported the synthetic method used to construct thirteen derivatives of 3-aryl/heteryl-2-cyanoacryloyl chloride followed by a focused survey on their spectral data and the synthetic importance of this scaffold for building a wide variety of heterocyclic skeletons using three different types of bidentate nucleophiles.

Keywords: Acryloyl chlorides; Activated nitrile; Bidentate Nucleophiles; Fused Heterocycles.

1. Introduction

Recently, 2-cyanopropenoyl chlorides have attracted a great attention due to their medicinal importance as a building block for various biological and pharmaceutical significant heterocyclic skeletons like benzimidazoles[1-3], benzoxazoles[4-6], benzothiazoles[7-9], benzoxazines[10], oxadiazoles[11], and pyrazoles[12], in addition to a wide variety of valuable fused heterocyclic systems (Fig. 1).In continuation to our program in the synthesis and biological screening of various heterocycles,[13-34] we summarized here the synthesis of target 3-aryl/hetaryl-2-cyanopropenoyl chlorides, their spectral data and their reaction routes with various bidentate nucleophiles.

2. Structure and its behaviour:

2.1. Spectral studies:

From the literature survey,[2-8] the IR spectra of the target acid chlorides showed the absorption bands for carbonyl group of the acid chloride at a range from ν 1738 to 1760 cm^{-1}, and the cyano functionality ranged from ν 2205 to 2228 cm^{-1}. Also, the ^1H NMR spectra showed signals for the olefinic proton at a range from δ 8.12 to 8.39 ppm, as well as the aromatic protons appeared at δ 6.50-8.50 ppm.

2.2. Behavior towards nucleophiles.

The 3-aryl/heteryl-2-cyanoacryloyl chloride derivatives **1** have from three electrophilic centers (a-c) which can be attacked by a variety of nucleophiles including oxygen, sulfur, and nitrogen (Fig. 2). Further course of the reaction behavior depends on the structure of initial reagent, the capacity of the nucleophile and the reaction conditions. Initially, the nucleophile attacks the most electron-deficient acid chloride group (a) followed by attacking on the positions (b) or (c) dependent on the nucleophilicity and stability of the products, producing heterocyclic derivatives.

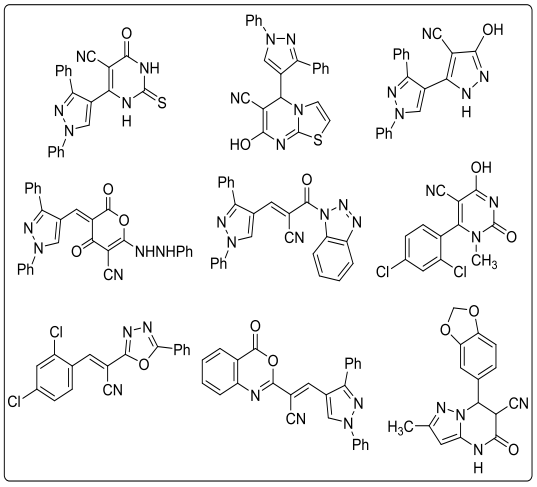

Fig. 1. Some heterocyclic skeletons derived from 2-cyanopropenoyl chlorides.

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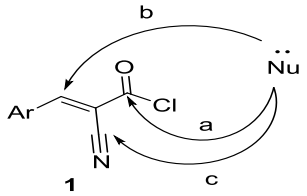


Fig. 2. Structure of the acid chlorides **1** and their behavior toward nucleophiles.

3. Synthesis of 3-aryl/heteryl-2-cyanoacryloyl chlorides

The most common method used for the preparation of 3-heteryl-2-cyanoacryloyl chloride derivatives is discussed as follows: Condensation of the aryl/heteryl aldehyde derivative **2** with ethyl cyanoacetate **3** afforded the corresponding arylidene derivative **4** which was easily transformed into the corresponding 3-aryl/hetaryl-2-cyanoacrylic acids **5** *via* hydrolysis using ethanolic sodium hydroxide solution (50 %) followed by acidification with dilute hydrochloric acid (20%). Treating the acrylic acid derivatives **5** with thionyl chloride acquired the targeted acid chlorides **6** (Scheme 1).[2-4,10-12]

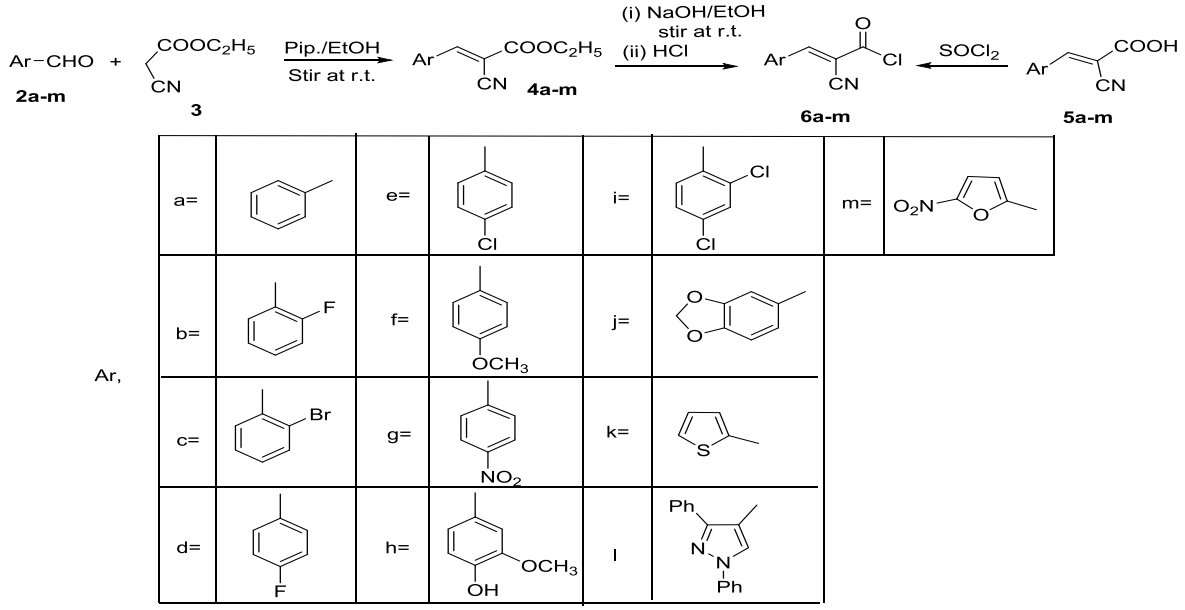
4. Reactions of 3-aryl-2-cyanoacryloyl chlorides with binucleophiles

In this work, the heterocycles constructed from the reaction of acryloyl chlorides with binucleophiles was summarized. Thus, the proclivity and behavior of the mentioned acid chloride **6** toward some 1,2-binucleophiles including hydrazine, phenylhydrazine and benzoylhydrazine, in addition to 1,3-binucleophiles like urea, thiourea, 2-aminopyridine and 2-aminothiazole, as well as 1,4-bidentate nucleophiles like 2-aminoaniline, 2-hydroxyaniline, 2-mercaptoaniline, 2-aminoethanol, thiosemicarbazide, and anthranilic acid, were studied thoroughly.

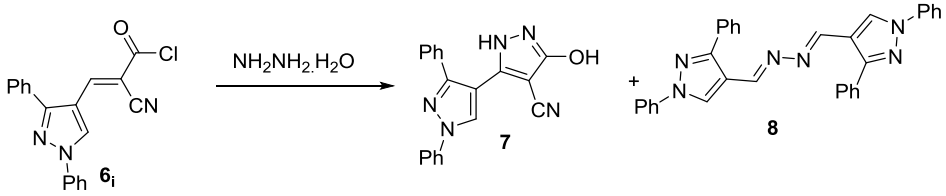
4.1. Reactions with 1,2-binucleophiles

4.1.1. Reaction with hydrazine hydrate

Hydrazinolysis of the acid chloride **6i** at 0 °C afforded a mixture of 5-hydroxy-1',3'-diphenyl-1'*H*,2*H*-[3,4'-bipyrazole]-4-carbonitrile **(7)** and diheterylazine derivative **8** (Scheme 2). Otherwise, hydrazinolysis of the other acid chloride derivatives afforded the azine derivatives **8** as a sole product and no pyrazole derivative was formed.[2-9]



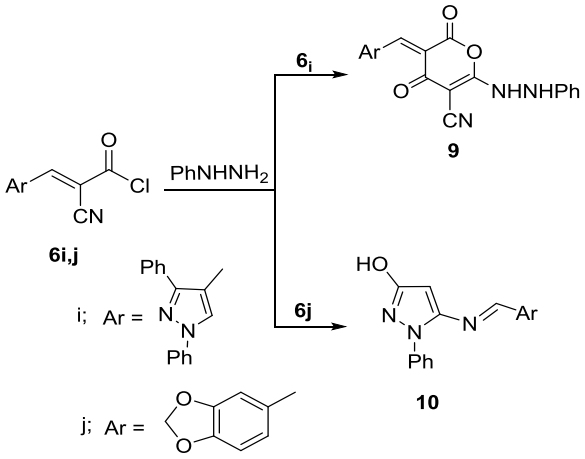
Scheme 1. Synthesized 3-aryl-2-cyanoacryloyl chlorides **6a-m**.



Scheme 2. Reaction of acryloyl chloride **61** with hydrazine hydrate.

4.1.2. Reaction with phenylhydrazine

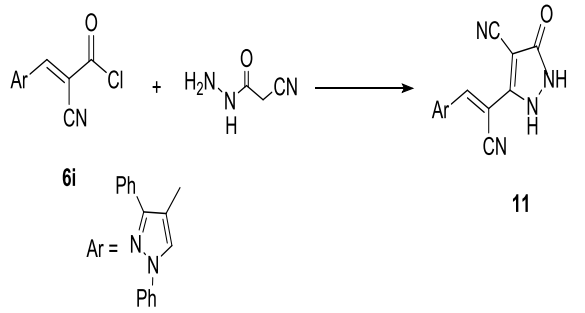
Reaction of the pyrazolyl acid chloride **6i** with phenylhydrazine in dioxane and triethylamine led to the construction of pyranedione derivative **9**.[2] While in case of the acid chloride **6j**, the pyrazol-3-ol derivative **10** was achieved (Scheme 3).[3]



Scheme 3. Reaction of acryloyl chlorides **6i-j** with benzoylhydrazine.

4.1.3. Reaction with 2-cyanoacetohydrazide

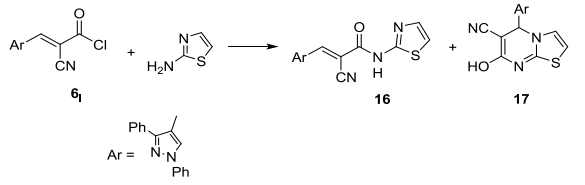
Interestingly, treating 2-cyanoacetohydrazide with the acid chloride **6l** afforded the pyrazolone derivative **11** (Scheme 4).[5]

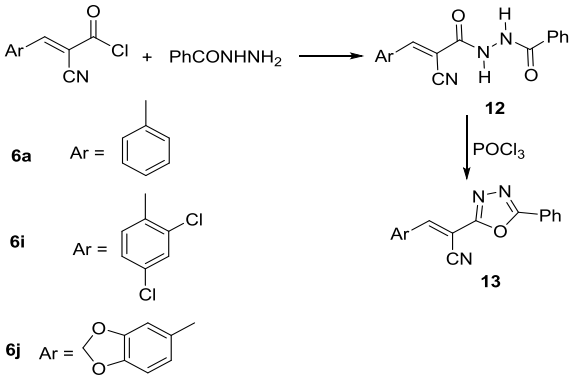


Scheme 4. Reaction of the acryloyl chloride **6i** with 2-cyanoacetohydrazide.

4.1.4. Reaction with benzoylhydrazine

On the other hand, reaction of acid chlorides **6a, 6i** and **6j** with benzoylhydrazine yielded *N,N'*-diacylhydrazine **12** which, upon heating with phosphorus oxychloride produced the corresponding dehydrating product, 1,3,4-oxadiazole derivative **13** (Scheme 5).[3,11,12]

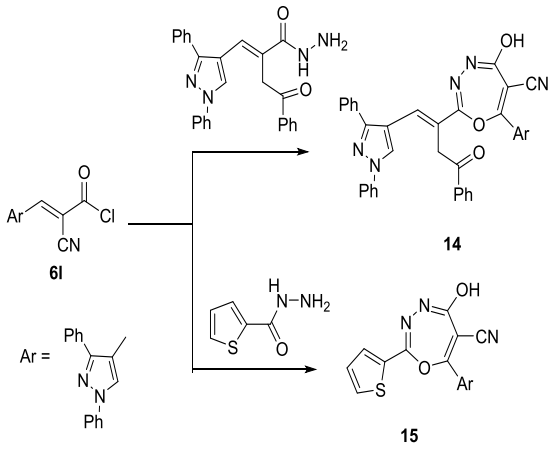




Scheme 5. Reaction of acid chlorides with benzoylhydrazine.

4.1.5. Reaction with hydrazides

Reaction of acid chloride **6l** with 2-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)-4-oxo-4-phenylbutanehydrazide or thiophene-2-carbohydrazide furnished the diazepine derivatives **14** and **15**, respectively (Scheme 6).[1]



Scheme 6. Reaction of acid chloride **6i** with acid hydrazides.

4.2 Reactions with 1,3-binucleophiles

4.2.1. Reaction with 2-aminothiazole

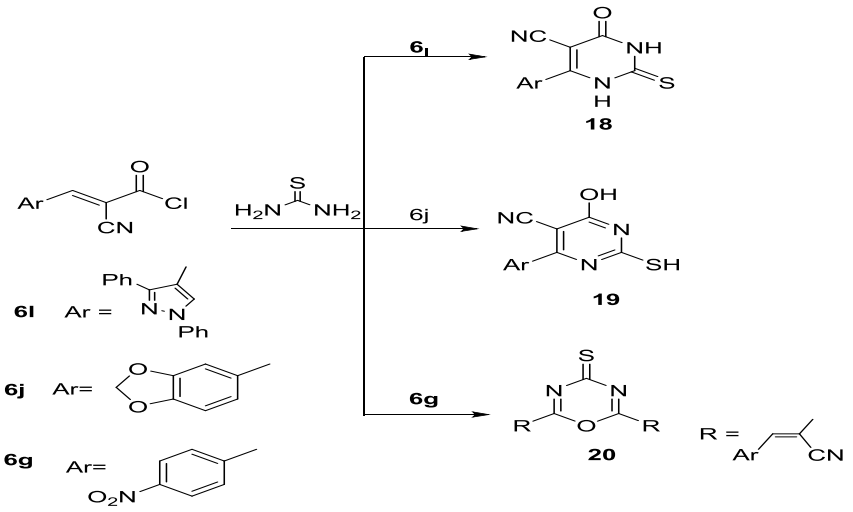
Treatment of the acid chloride **6l** with 2-aminothiazole in refluxing benzene and triethylamine as a base catalyst afforded the amide derivative **16** and thiazolopyrimidine **17** (Scheme 7).[2]

Scheme 7. Reaction of acid chloride **6i** with 2-aminothiazole.

4.2.2. Reaction with thiourea

In turn, conducting the acid chloride **6i** with thiourea acquired the pyrimidinethione derivative **18**.[2] In turn, condensation of the acid chloride **6j**

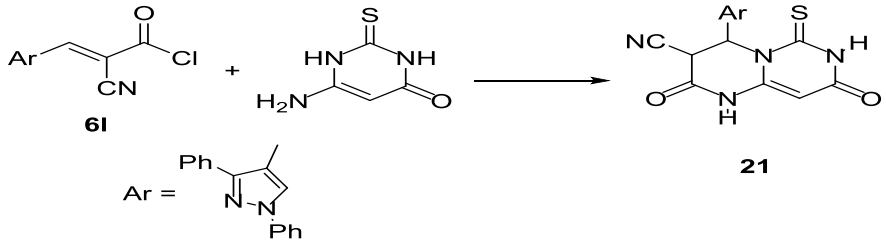
with thiourea in the presence of triethylamine gave the pyrimidine derivative **19**.[3] 2-Cyano-3-(4-nitrophenyl)-2-propenoyl chloride **6g** condensed with thiourea to give 1,3,5-oxadiazine derivatives **20** (Scheme 8).[35]



Scheme 8. Reactions of the acid chlorides with thiourea.

4.2.3. Reaction with 6-aminothiouracil

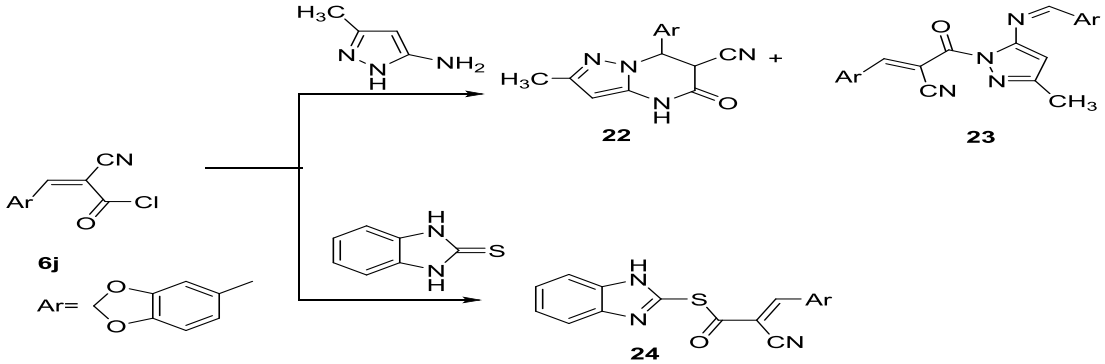
Otherwise, the pyrimidopyrimidine derivative **21** was commenced from the reaction of acid chloride **6l** with 6-aminothiouracil in refluxing dioxane and triethylamine (Scheme 9).[2]



Scheme 9. Reaction of the acid chloride **6i** with 6-aminothiouracil.

4.2.4. Reaction with 5-amino-3-methyl-1H-pyrazole or benzimidazolethione

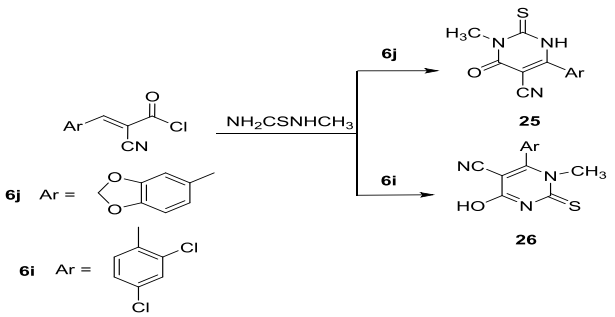
Condensation of **6j** with 1,3-binucleophilic reagents like, 5-amino-3-methyl-1*H*-pyrazole yielded a mixture of the fused heterocyclic compounds, pyrazolo[1,5-a]pyrimidine-5-one derivative **22** and pyrazole derivative **23.** While, interaction of **6j** with benzimidazolethione in boiling dioxane and/or heating without solvent at 140 ºC afforded the thioester derivative namely, *S*-1*H*-benzo[*d*]-imidazol-2-yl-3-(benzo[*d*][1,3]dioxol-5-yl)-2-cyanoprop-2-enethioate **(24).** (Scheme 10).[3]



Scheme 10. Reaction of the acid chloride **6j** with 5-amino-3-methyl-1*H*-pyrazole or benzimidazolethione.

4.2.5. Reaction with N-methylthiourea

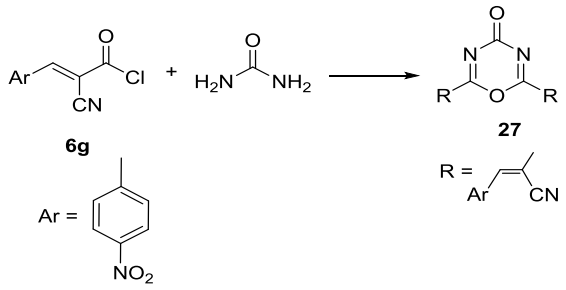
In turn, treating the acid chloride **6j** with *N*-methylthiourea acquired the pyrimidinethione derivative **25**.[3] Condensation of the acid chloride **6i** with methylthiourea in dry benzene and triethylamine gave the pyrimidinethione derivative **26** (Scheme 11).[12]



Scheme 11. Reactions of the acid chlorides with methylthiourea.

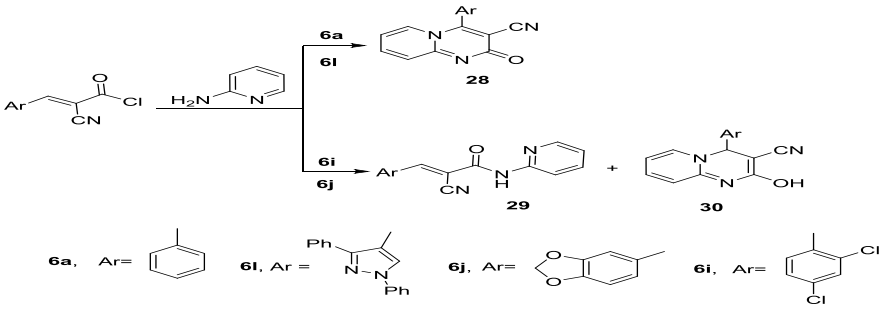
4.2.2. Reaction with urea

2-Cyano-3-(4-nitrophenyl)-2-propenoyl chloride **6g** condensed with urea to give 1,3,5-oxadiazine derivatives **27** (Scheme 12).[35]



Scheme 12. Reaction of acid chloride **6g** with urea

It was worthy that, interaction of the acid chloride **6a,l** with 2-aminopyridine furnished the fused heterocyclic product, pyrido[1,2-*a*]pyrimidine derivative **28** as a sole product.[1,10] Otherwise, such a reaction of the acid chloride **6j** or **6i** afforded a mixture of *N*-(pyridine-2-yl)acrylamide **29** and pyrido[1,2-a]pyrimidine derivative **30**. (Scheme 13).[3,12]

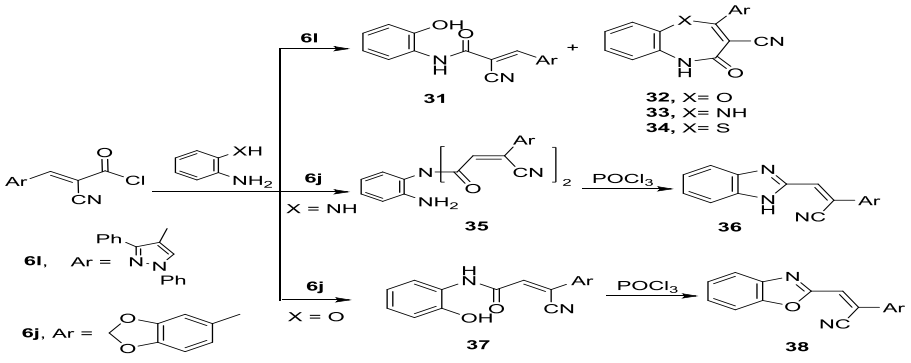


Scheme 13. Reaction of acid chlorides with 2-aminopyridine.

4.3. Reactions with 1,4-binucleophiles

4.3.1. Reactions with 2-hydroxy-, 2-amino- or 2-mercapto-aniline

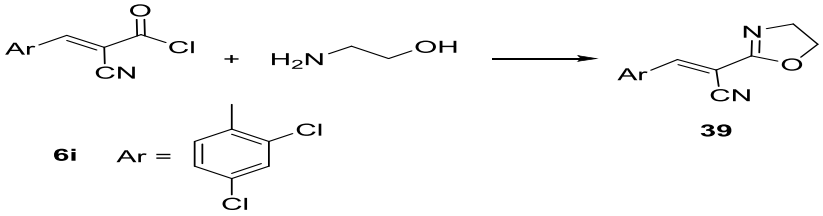
Treating **6l** with 2-hydroxyaniline afforded a mixture of acrylamide derivative **31** and benzoxazepine derivative **32**. Such a reaction with 2-aminoaniline or 2-mercaptoaniline acquired the benzodiazepine **33** and benzothiazepine **34**, respectively (Scheme 14).[2] On contrary, the benzimidazole **36** and benzoxazole **38** derivatives were reported *via* interaction of **6j** with 2-aminoaniline or 2-hydroxyaniline, respectively, followed by heating with phosphorus oxychloride (Scheme 14).[3]



Scheme 14. Reaction of acid chlorides with 2-aminophenol, 2-aminoaniline, and 2-aminothiophenol.

4.3.2. Reaction with 2-aminoethanol

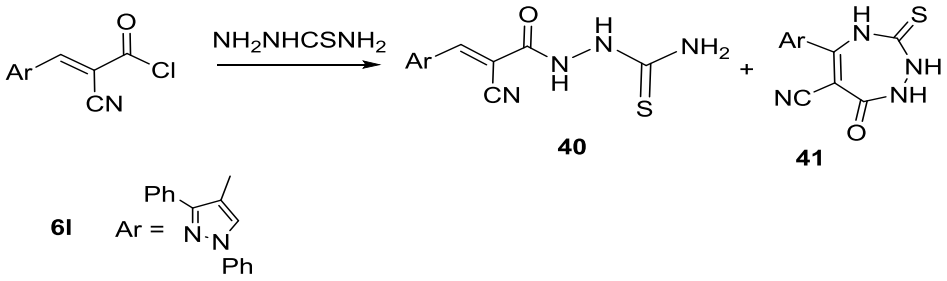
The 2-oxazoline derivative **39** was synthesized *via* conducting the acid chloride **6i** with 2-aminoethanol under basic conditions (Scheme 15).[12]



Scheme 15. Reaction of acid chlorides with 2-aminoethanol.

4.3.3. Reaction with thiosemicarbazide

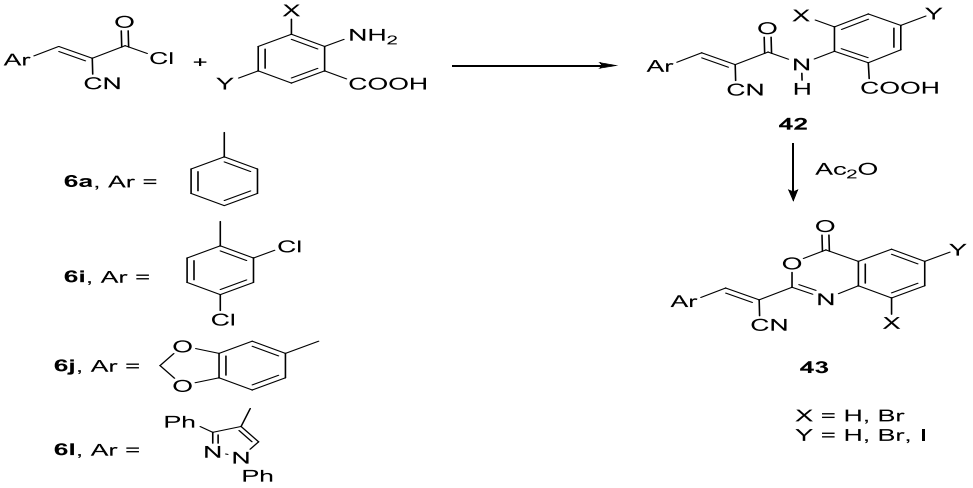
Treating the acid chloride **6l** with thiosemicarbazide furnished a mixture of thiosemicarbazide derivative **40** and triazepinethione derivative **41**, which were separated by fractional recrystallization (Scheme 16).[2]



Scheme 16. Reaction of acid chloride **6l** with thiosemicarbazide.

5. Conversion into benzoxazinone derivatives

Noteworthy, the acid chlorides **6** have been successfully transformed into benzoxazinone derivatives **43** *via* its treating with anthranilic acid or its derivatives under basic conditions affording the benzamide derivatives **42** followed by ring closure using acetic anhydride (Scheme 17).[1-3, 10-12]



Scheme 17. Reaction of acid chlorides with anthranilic acid derivatives.

Conflicts of Interest:

The authors declare no conflicts of interest.

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