SYNTHESIS OF 2-(CHLOROMETHYL)BENZOYL CHLORIDE AND ITS REACTIONS WITH NUCLEOPHILES

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Introduction

The chemistry and reactivity of the isoindolinone ring system are currently an area of interest for many research groups due to its biological activity. It has been recognized that *N*-substituted isoindolinones and their 3-substituted derivatives possess anxiolytic activity and are of interest as sedatives, hypnotics and muscle relaxants [1], including the anxiolytic [2] and the anxiolytic/anticonvulsant [3]. It was found that *N*-substituted isoindolinones (**11**) are constituents of antihypertensive [4], antiphlogistic [5] and analgesic [6] medicinal drugs and are substrates in the synthesis of different medicines [7] and natural products [8]. Other bioactive isoindolinones include the 5-HT antagonists [9] and the non-nucleosidic HIV-reverse transcriptase inhibitors [10].

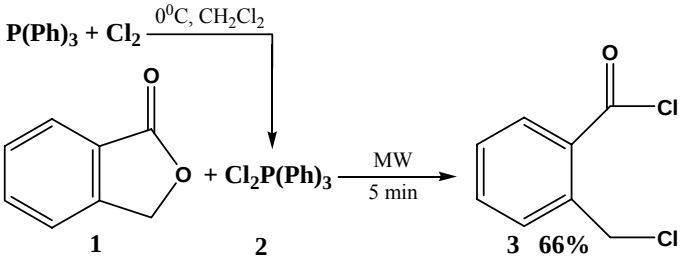
In this article we report results of our studies on the synthesis of 2-(chloromethyl)benzoyl chloride (**3**) and its reactions with primary aliphatic and aromatic amines, *CH*-acids and *S*-nucleophiles.

Results and Discussion

*Synthesis of 2-(chloromethyl)benzoyl chloride (**3**)*

2-(chloromethyl)benzoyl chloride (**3**) plays an important role in synthesis of many different organic compounds. In this work, we present alternative method for earlier known synthesis of this compound.

Our method is based on the reaction of *3H*-isobenzofuran-1-one (**1**) with dichlorotriphenylphosphine (**2**) obtained from triphenylphosphine chlorinated with dry, gaseous chlorine in dry dichloromethane as shown in scheme 1. This reaction was carried out under cooling in the ice/salt bath until all substrate reacted. When the reaction was completed, dichloromethane was evaporated *in vacuo* and the reaction has been continued in the microwave (400 W) for 5 minutes. 2-(chloromethyl)benzoyl chloride (**3**) was distilled off *in vacuo* from the residue as colourless oil.



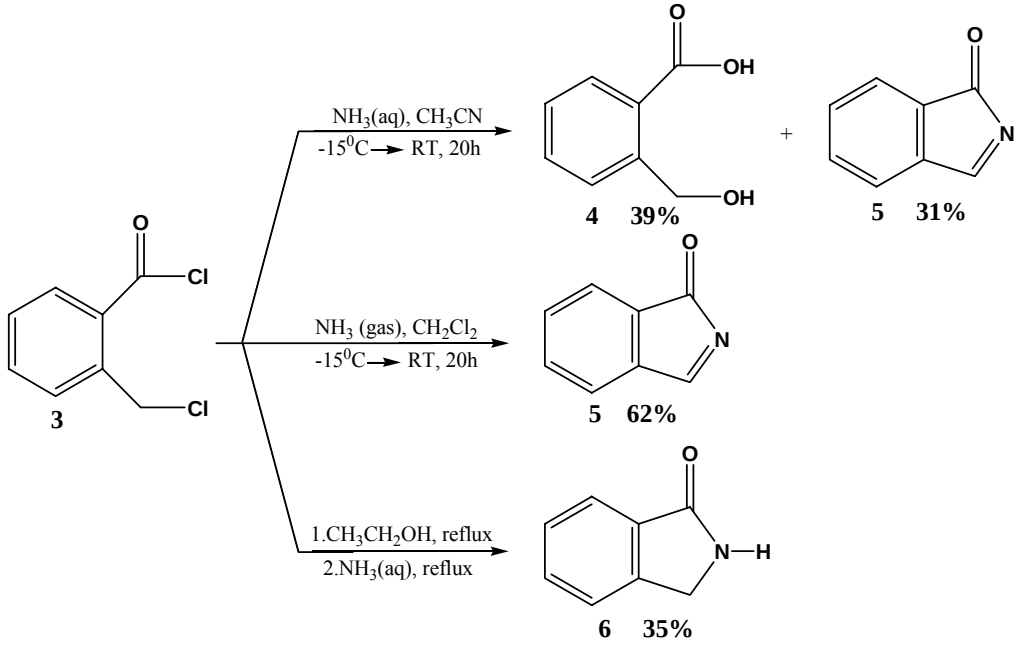
Scheme 1. Synthesis of 2-(chloromethyl)benzoyl chloride (**3**)

*Reaction of 2-(chloromethyl)benzoyl chloride (**3**) with N-nucleophiles*

2-(chloromethyl)benzoyl chloride (**3**) can act as *bis*-electrophile with one electrophilic center localized on the carbonyl atom and the second localized on the carbon. Both of these centers can compete toward nucleophile such as for example amine nitrogen, and finally give *N*-substituted isoindolinones (**11**).

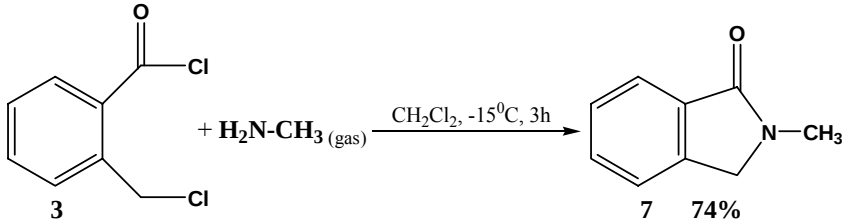
When a water solution of ammonia was a reagent, 2-(hydroxymethyl)benzoic acid (**4**) and benzisoindolone (**5**) were produced. The compound **5** was obtained as a sole product, when vigorously stirred, cooled on ice/salt bath solution of 2-(chloromethyl)benzoyl chloride (**3**) in dry dichloromethane was saturated by dry, gaseous ammonia over 30 min.

Isoindolin-1-one (**6**) was obtained by heating of 2-(chloromethyl)benzoyl chloride (**3**) in ethanol followed by treatment with aqueous ammonia (scheme 2).



Scheme 2. Reaction of 2-(chloromethyl)benzoyl chloride (**3**) with ammonia

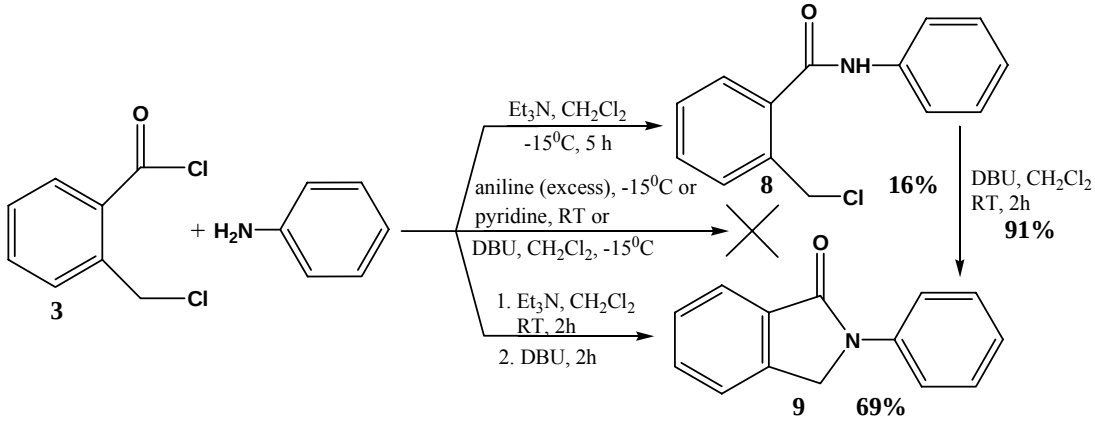
The reaction of dichloride (**3**) with methylamine gave 2-methylisoindolin-1-one (**7**) as shown in scheme 3, while the similar reaction with aniline in the presence of triethylamine led to 2-(chloromethyl)-*N*-phenylbenzamide (**8**). In the next step compound **8** treated with DBU gave stable *N*-phenylisoindolin-1-one (**9**) as final product.



Scheme 3. Reaction of 2-(chloromethyl)benzoyl chloride (**3**) with methylamine

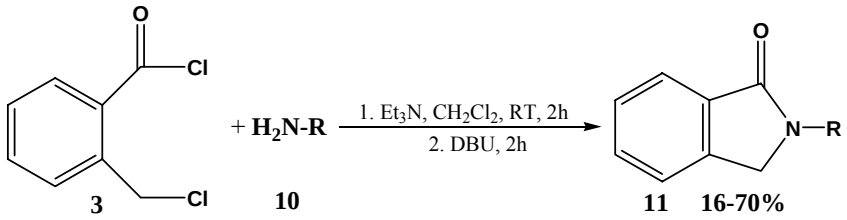
One observed, that aniline in the reaction with 2-(chloromethyl)benzoyl chloride (**3**) in excess aniline, pyridine or in attendance DBU gives mixtures of many unstable products.

Only two-step, one-pot reaction 2-(chloromethyl)benzoyl chloride (**3**) with aniline in the presence of triethylamine and then DBU gave *N*-phenylisoindolin-1-one (**9**) in a high yield (scheme 4).



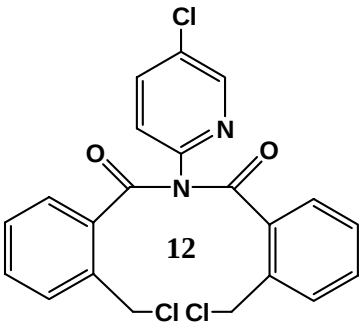
Scheme 4. Reaction of 2-(chloromethyl)benzoyl chloride (**3**) with aniline

This method, having a general synthetic value, was applied for synthesis of several different *N*-substituted benzisoindolinones (**11**) as shown in scheme 5.



R= 4-C_6H_4Cl, 2-(5-C_5H_3NCl), $N(Ph)_2$, 2-C_5H_4N, $CH_2CH_2CH_3$, CH_2Ph, SO_2-4-$C_6H_4CH_3$

Scheme 5. Reaction of 2-(chloromethyl)benzoyl chloride (**3**) with amines (**10**)



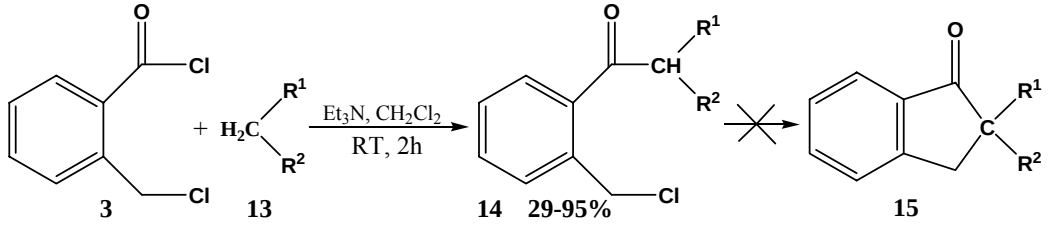
When dichloride (**3**) was treated with 5-chloropyridin-2-amine, 2-(5-chloropyridin-2-yl)iso-indolin-1-one (**11**) R=2-(5-Cl-C_5H_3N) and compound (**12**) (39%) were isolated on the silica gel column.

The urea, thiourea, ethane-1,2-diamine and acetamide in the reaction with 2-(chloromethyl)-benzoyl chloride (**3**) give only complex mixtures of unstable products.

Figure 1.

*Reaction of 2-(chloromethyl)benzoyl chloride (**3**) with CH-acids (**13**)*

The compounds **13**, having methylene group activated by two electron-withdrawing substituents easily underwent acylation, and mono substituted 2-(chloromethyl)benzoyl chlorides (**14**), presented in scheme 6, were formed. The compounds **14** in the presence of bases such as Et_3N, DBU, K_2CO_3, NaH and LDA/CH_2Cl_2 did not undergo intramolecular alkylation. When compound **14** was treated with LDA in THF, *n*-butyl 2-(chloromethyl)benzoate was produced.

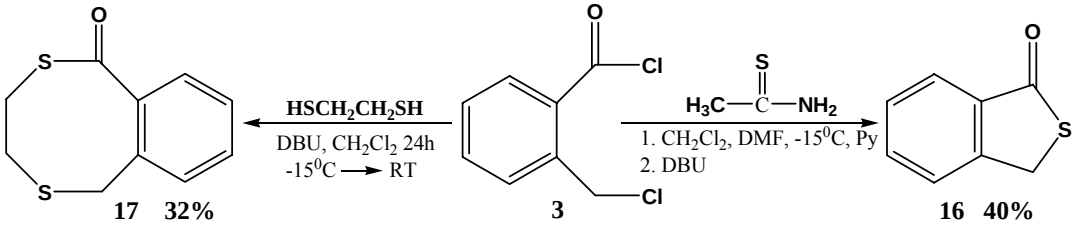


R^1-R^2= -C(=O)$CH_2C(CH_3)_2CH_2C$(=O)-; -C(=O)$(CH_2)_n$C(=O)-, n=2,3
R^1= CN, R^2= C(=O)Ph

Scheme 6. Reaction of 2-(chloromethyl)benzoyl chloride (**3**) with *CH*-acids (**13**)

*Reaction of 2-(chloromethyl)benzoyl chloride (**3**) with S-nucleophiles*

Benzo[*c*]tiophen-1-(*3H*)-one (**16**) was obtained by the treatment of 2-(chloromethyl)benzoyl chloride (**3**) with ethanethioamide, but the reaction of the same dichloride (**3**) with ethane-1,2-dithiol gave eight-membered macrocycle **17** (scheme 7).



Scheme 7. Reaction of 2-(chloromethyl)benzoyl chloride (**3**) with *S*-nucleophiles

Biological tests

All N-substituted isoindolin-1-ones have been tested against selected viruses (HSV-1, EMCV, VSV) as control compounds for highly active group of benzisoselenazol-3(2H)-ones, same way as previously reported [11]. We hypothesized that antiviral activity of selenoorganic compounds was related to the presence of selenium. Thus, we designed compounds in which selenium has been replaced by methylene group and tested them in the same conditions as selenic compounds. As we suppose, isoindolin-1-ones didn't exhibit any antiviral activity what confirmed our hypothesis.

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