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The unusual reaction of 2-isocyanatophenyl acetate with amines and water

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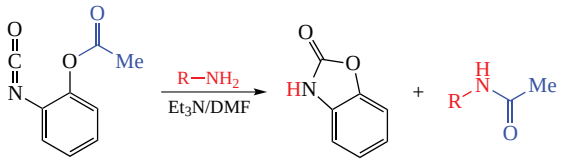
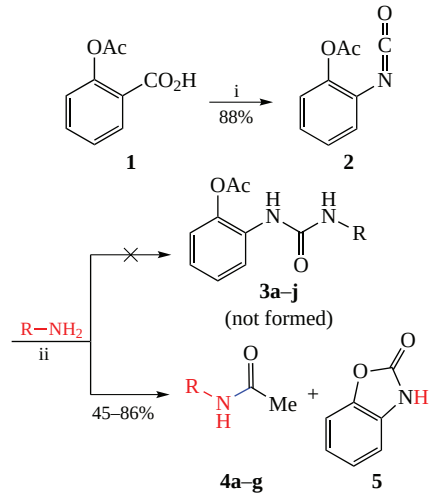
The reaction of 2-isocyanatophenyl acetate with adamantyl- and phenyl-containing amines gave the corresponding acetamides. Intermediate 2-isocyanatophenol formed in the course of the reaction undergoes intramolecular cyclization to 2-benzoxazolinone. These reactions proceed only with amines possessing basicity (pK_b > 3.80).



Keywords: 2-isocyanatophenyl acetate, acetamides, ureas, acetylsalicylic acid, 2-benzoxazolinone.

Preparations containing ureido group are currently used as antiviral,[1] anti-inflammatory agents[2] and drugs for the treatment of infectious diseases[3] and cancer.[4,5] Substituted ureas are studied as potential drugs for the treatment of neuropathic pain and inflammatory conditions. The target for such molecules is soluble epoxide hydrolase (sEH, E.C. 3.3.2.10), an enzyme involved in the metabolism of arachidonic acid.[6,7] However, in addition to soluble epoxide hydrolase, other enzymes are also involved in the 'arachidon cascade', such as prostaglandin-endoperoxide synthase 1 and 2 (PTGS1/COX-1, PTGS2/COX-2, EC 1.14.99.1), a family of isoenzymes responsible for the formation of prostanoids, including thromboxane and prostaglandins such as prostacyclin, from arachidonic acid.[8,9] Inhibition of PTGS may relieve symptoms of pain and inflammation.[8] One of the best known PTGS inhibitors is acetylsalicylic acid (aspirin) **1**.



a R = 2-adamantyl
b R = (1-adamantyl)methyl
c R = 1-(1-adamantyl)ethyl
d R = Ph
e R = 4-FC_6H_4
f R = *n*-C_6H_{13}
g R = Pr
h R = 2-FC_6H_4
i R = 2,4-$F_2C_6H_3$
j R = 2,6-$F_2C_6H_3$

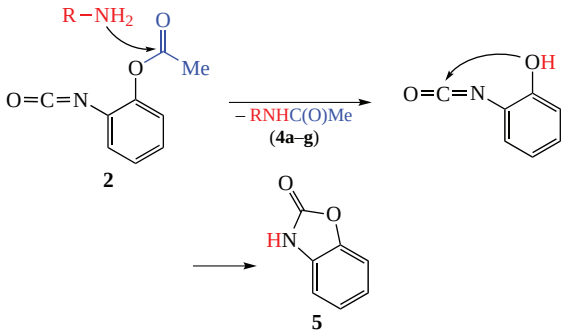
Scheme 1 *Reagents and conditions*: i, $(PhO)_2P(O)N_3$ (DPPA), Et_3N, toluene, 110 °C, 2 h; ii, Et_3N, DMF, room temperature, 12 h.

The synthesis of biologically active compounds based on known drugs when they are used as intermediates is a promising direction in medicinal chemistry. Such an example is *N*-(1-adamantyl)-2-(2-dimethylaminoethoxy)acetamide (tromantadine), an antiviral agent against the Herpes zoster[10] virus, which is a derivative of adamantan-1-amine (amantadine), another antiviral and at the same time an antiparkinsonian agent.

Previously, we reported on the synthesis of ureas containing a fragment of another known drug, 2-(4-isobutylphenyl)propionic acid (ibuprofen).[11] In this regard, we have made attempts to synthesize ureas containing a fragment of the aspirin molecule (Scheme 1). 2-Isocyanatophenyl acetate **2** was obtained from acetylsalicylic acid **1** and diphenyl phosphorazidate (DPPA) as the reagent for the Curtius reaction[12] (step i). To obtain 1,3-disubstituted ureas **3**, compound **2** was reacted with aromatic and adamantyl-containing amines (step ii).

However, NMR and MS study of the crude products showed that anticipated 1,3-disubstituted ureas **3a**–**j** could not be obtained. Generally, acetamides **4a**–**g** and 2-benzoxazolinone **5** were formed (see Scheme 1), while 2-fluoro-, 2,4-difluoro- and 2,6-difluoroanilines remained unchanged. Apparently, in the course of the reaction 2-isocyanatophenyl acetate **2** acts as the acyl donor to initially form acetamides **4a**–**g** and 2-isocyanatophenol (Scheme 2). The latter would spontaneously cyclize into 2-benzoxazolinone **5**.

The literature[13] describes the preparation of a series of 1,3,3-trisubstituted ureas by the reaction of 2-cyanoaziridine-1-



Scheme 2

carboxamide with various isocyanates in yields up to 94%. However, in the case of 2-isocyanatophenyl acetate **2** the yield of the urea derivative was only 10%, which may be associated with the formation of the corresponding acetamide and 2-benzoxazolinone **5** as the main reaction products.

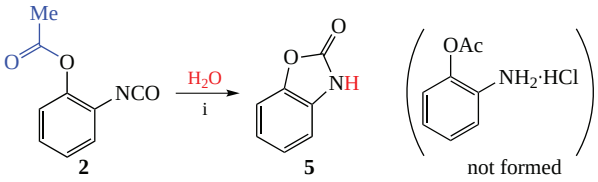
Not all amines are capable of being acylated with 2-isocyanatophenyl acetate **2**. The electron-donating adamantyl radical increases the electron density on the nitrogen atom, and the formation of acetamides proceeds easily. Arylamines are weaker bases, and those containing fluorine atoms in the aromatic ring are even weaker. Of them, only 4-fluoroaniline reacts with 2-isocynatophenyl acetate **2** to form anilide **4e** in 45% yield, whereas 2-fluoro-, 2,4-difluoro- and 2,6-difluoroanilines remain intact. The fluorine atom in the *para* position of 4-fluoroaniline has little effect on the amino group of the molecule not significantly lowering its basicity (see Online Supplementary Materials, Figure S1). On the contrary, in the molecules of other fluorinated anilines the effect of fluorine atom(s) is much more pronounced. The melting points and mass spectra of the obtained *N*-phenylacetamide and 4-fluorophenylacetamide coincide with the literature data.[14]

Aliphatic *n*-propylamine and *n*-hexylamine have the same basicity and are readily acylated with 2-isocyanatophenyl acetate **2** to form the corresponding acetamides **4g**,**f**. The melting points and mass spectra of the obtained *n*-propylacetamide **4g** and *n*-hexylacetamide **4f** coincide with the literature data.[15,16]

It is known[17] that aromatic isocyanates containing an ester group may be cyclized by the Wittig reaction using 3-methyl-1-phenyl-2-phospholene 1-oxide as the catalyst. During that reaction, substituted benzoxazoles are formed, which differ in structure from the herein obtained 2-benzoxazolinone **5**. Acylation of amines with aspirin **1** itself was also described, however, the resulting salicylic hydroxy acid did not undergo further transformations.[18]

It is of note that in our case, 2-benzoxazolinone **5** is formed not only in basic medium but also in an acid one. An attempt was made to obtain the corresponding amine hydrochloride from 2-isocyanatophenyl acetate **2** by the reaction with hydrochloric acid in toluene (Scheme 3). However, only 2-benzoxazolinone **5** was obtained in 92% yield.

Possible pathways of the reaction and the proposed mechanism are discussed in detail in Online Supplementary Materials. The course of the reaction is consistent with the calculations of the potential energies of formation of molecules for all possible intermediates involved in specific transformations (Figure 1). Calculations were performed using the Avogadro program: an open-source molecular builder and visualization tool, version 1.2.0 http://avogadro.cc/.[19] The potential energy of formation of the heterocyclic product is less than the energy of the formation of 2-aminophenyl acetate from carbamic acid (see Online Supplementary Materials, Schemes S1 and S2). In turn, the energy of the formation of carbamic acid is greater than the energy of the formation of 2-isocyanatophenol, which indicates the impossibility of hydrolysis in the isocyanate group. The most energetically favorable is the formation of 2-isocyanatophenol followed by its cyclization to 2-benzoxazolinone **5**. As a result,



Scheme 3 *Reagents and conditions*: i, HCl conc., toluene, room temperature, 12 h.

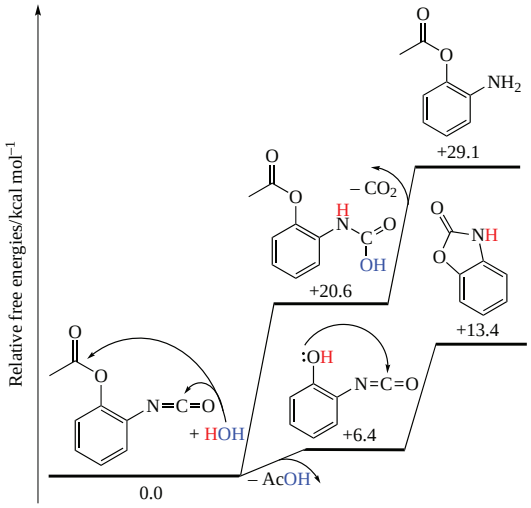


Figure 1 Free energy profile for hydrolysis reactions of 2-isocyanatophenyl acetate.

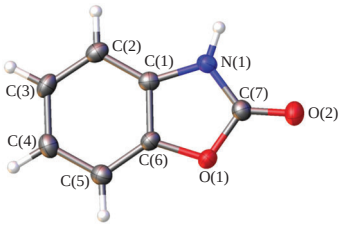


Figure 2 ORTEP diagram showing 50% probability anisotropic displacement ellipsoids of non-hydrogen atoms for compound **5** according to single crystal XRD data collected at 100.0(4) K.

we may conclude that the ester bond is hydrolyzed first; therefore, the reaction of 2-isocyanatophenol with hydrochloric acid proceeds as shown in Scheme 3.

The structure of 2-benzoxazolinone **5** was confirmed by X-ray diffraction analysis (Figure 2).† These data coincide with the literature ones.[20]

In summary, an unusual reaction of 2-isocyanatophenyl acetate with amines was discovered, leading to acetamides and 2-benzoxazolinone. The mechanism of the reaction is proposed and the potential energies of formation of all possible intermediates involved in specific transformations are calculated.

† *Crystal data for* **5**. $C_7H_5NO_2$ (M = 135.12), orthorhombic, space group $P2_12_12_1$ at 100.0(4) K, a = 4.38370(10), b = 6.5659(2) and c = 20.7395(6) Å, V = 596.94(3) Å^3, Z = 4, d_{calc} = 1.503 g cm^{-3}, μ(CuKα) = 0.947 mm^{-1}, F(000) = 280.0. Total of 3247 reflections were collected [1248 independent reflections with wR_2 0.0969, GOOF 1.082 for all independent reflections, R_1 = 0.0374 was calculated for 1248 reflections with $I > 2\sigma(I)$].

X-ray diffraction data were collected on an XtaLAB Synergy (Oxford Diffraction) diffractometer equipped with a CCD detector HyPix-6000, using CuKα-radiation (1.54184 Å) and Cryosteam crystal temperature control system (Oxford Cryosystems). During the survey, a four-circle KAPPA goniometer was used in the scanning mode along the ω axis with a step of 1°, the interval of diffraction angles 2θ = 7–145°, and a complete array of diffraction data was collected. The crystal was collected under a binocular microscope and mounted in a nylon CryoLoop (Hampton Research) using Paratone-N cryo-oil (Hampton Research). Primary processing of experimental data was performed using the CrysAlisPro software package (Agilent Technologies). The absorption correction was introduced using the SCALE3 ABSPACK algorithm integrated into the CrysAlisPro package. The structure was deciphered and refined with the Olex2 program using the SHELX software package.[21]

CCDC 2152192 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2022.09.039.

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