JOURNAL OF CHEMICAL EDUCATION

Laboratory Experiment

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Synthesis of 3-Methyl-4-(4-methylbenzoyl)-1-phenyl-pyrazol-5-one: How To Avoid O-Acylation

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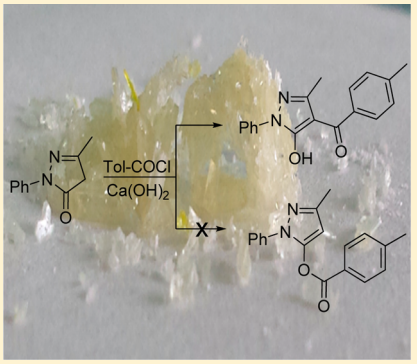
Supporting Information

ABSTRACT: In this laboratory experiment, students synthesize 3-methyl-4-(4-methylbenzoyl)-1-phenyl-pyrazol-5-one by selective C-acylation of 3-methyl-1-phenyl-1*H*-pyrazol-5-one. Calcium hydroxide is used to push the tautomeric equilibrium toward the enol form, to protect the hydroxyl functionality as a complex, to trap the liberated hydrogen chloride, and to keep the reaction media basic. The product is obtained in excellent yield and recrystallized from various solvents and solvent systems. The chromatographic and physical parameters are determined and the results are analyzed. The signals in the NMR spectra of acyl pyrazolone are assigned and then compared with those of three previously synthesized acyl pyrazolones and two corresponding O-acylated products.



KEYWORDS: *Second-Year Undergraduate, Organic Chemistry, Analytical Chemistry, Laboratory Instruction, Hands-On Learning/Manipulatives, Heterocycles, NMR Spectroscopy, Synthesis*

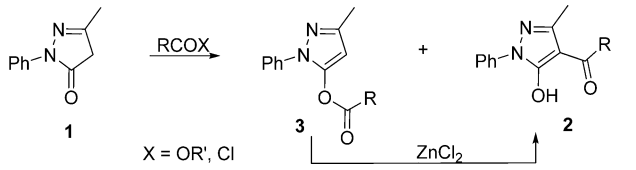
IN TRODUCTION

4-Acylpyrazol-5-ones are among the most widely exploited O-donors in coordination chemistry.[1] First studied by Jensen,[2] the chelating behavior of this class of β-dicarbonyl compounds have received immense attention due to several valuable properties, such as lower pK_a values in comparison with conventional β-dicarbonyl compounds, vast extracting ability, great separation power, and intense color of their complexes. In particular, aroyl pyrazolones have displayed great complexation and extraction ability toward metal ions, including 4f- and 5f-elements,[3] which were found to be strongly dependent on the place and nature of the substituent in the aromatic ring of the acyl group, i.e., on the electronic, steric, and solubility parameters of the ligand.

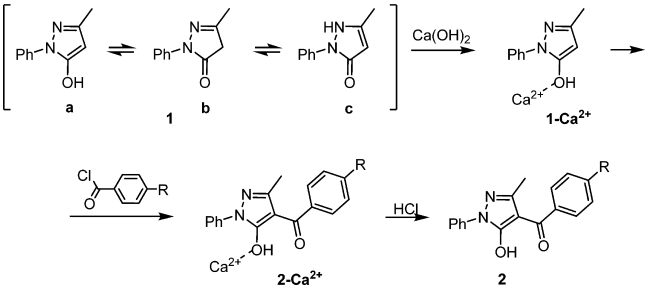
Acylpyrazolones have been known since the end of the 19th century. The initial synthetic strategies have been based on classical Claisen condensation of esters with pyrazolone catalyzed by sodium salts of acids or sodium ethoxide, or on Fries rearrangement of O-acylated pyrazolones to C-acylated products by anhydrous zinc chloride (Scheme 1).[4] However, both protocols have suffered with drawbacks such as low yields and colored side-products.

An advantageous fast and efficient protocol was developed in 1959 by Jensen,[5] and, practically, has no concurrence and has been intensively exploited. The method is based on direct acylation of pyrazolones with acyl chlorides or anhydrides in the presence of calcium hydroxide (Scheme 2). However, calcium hydroxide does not "catalyze" the reaction as claimed in the original work; it plays a crucial versatile role to perform the transformation successfully.

Scheme 1. Initial Protocols for the Preparation of 4-Acyl Pyrazolones



Scheme 2. Jensen's Protocol for C-Acylation of Pyrazolones



To achieve C-acylation at the fourth position of pyrazolone, two factors have to be taken into account. First, the starting pyrazolone has to be in the enol form (**1a**) to activate the fourth position. Second, the OH group has to be protected to avoid O-acylation. Calcium hydroxide makes the required pH needed to form the enol and also complexes[6] with the hydroxyl

dx.doi.org/10.1021/ed5000636 | J. Chem. Educ. XXXX, XXX, XXX−XXX

functionality. Additionally, 2 equiv are used to trap the liberated hydrogen chloride, and thus keep the media basic and avoid the decomposition of the complex during the acylation reaction.

From a synthetic point of view, it is very important to form the calcium complex before acylation. If the acylating agent is added immediately after calcium hydroxide, the corresponding ester is the only or main reaction product. The latter has never been mentioned in the literature.

This particular laboratory experiment meets the goals of providing students with practical experience in regioselective acylation of heterocyclic compounds, namely, pyrazolones, and acquiring skills in interpreting 1D and 2D NMR spectra. Students were involved in the project in the frame of a European program for students' practices aiming to improve the practical skills of students by extra laboratory exercises in scientific institutions; eight second-year undergraduate students enrolled in fine organic synthesis (September−December 2013, 240 h each) completed the experiment. The syntheses were accomplished in pairs followed by individual recrystallizations from different solvents, determination of chromatographic and physical parameters, and NMR exercises.

EXPERIMENTAL OVERVIEW

The experiment is a one-pot protocol for selective C-acylation of 3-methyl-1-phenyl-1*H*-pyrazol-5-one by an acid chloride. The aim is to obtain acyl pyrazolone without the corresponding ester impurity, the O-acylation product. *p*-Toluoyl chloride was selected because it reacts with pyrazolone faster than the other acid chlorides studied, 1.5 vs 2−9 h. The experiment can be completed in less than 6 h over two laboratory periods.

EXPERIMENT

Each laboratory session starts with careful reading of MSDS certificates of all reagents and solvents that are used.

The reaction is carried out in dry dioxane in a three-step sequence (Scheme 2). The starting pyrazolone is fully dissolved in dioxane by gentle heating, and $Ca(OH)_2$ is added. The suspension is refluxed with stirring until complete formation of the complex as followed by TLC on basic alumina. It is very important to form the complex before the addition of the acylating agent in order to avoid O-acylation. The pale yellow heterogeneous mixture is cooled, and *p*-toluoyl chloride is added dropwise at 0 °C and refluxed. Acylation is followed by TLC on silica gel. The orange mixture is cooled to room temperature and slowly added to 10% aq HCl with vigorous stirring to avoid formation of lumps. The latter hinders the decomposition of the complex and can result in a decrease of the product yield. The solid phase formed is filtered off after 1.5 h or during the next day, which has negligible influence on the reaction yield. The crude product is air-dried, an aliquot is saved, and the remaining product is recrystallized from methanol−acetone to afford the pure compound as white plates. A detailed procedure is given in the Supporting Information.

In the second part of the laboratory work, students characterize and recrystallize the product from different solvents. Pure 3-methyl-4-(4-methylbenzoyl)-1-phenyl-pyrazol-5-one and the crude product are analyzed by TLC on silica gel using various mobile phases. The pure product is recrystallized a second time from different solvents, e.g., heptane, acetone, alcohols, and mixed solvents, in order to obtain the compound as yellow crystals from nonpolar solvents and colorless crystals from polar solvents.[4b,7] Each student performs six recrystallizations. The melting points of the crystals are determined.

Students obtain NMR spectra of their product, 3-methyl-4-(4-methylbenzoyl)-1-phenyl-pyrazol-5-one. The assignment of the signals in proton and carbon spectra is performed by analyzing the interaction in 2D experiments. The tautomeric preferences are studied.[8] To understand the influence of the type and position of the substituent on the NMR signal's pattern and chemical shift, the spectra of 3-methyl-4-(4-fluorobenzoyl)-1-phenyl-pyrazol-5-one, 3-methyl-4-(4-phenylbenzoyl)-1-phenyl-pyrazol-5-one, and 3-methyl-4-(3-methylbenzoyl)-1-phenyl-pyrazol-5-one, as well as those of 4-methylbenzoyl and 4-fluorobenzoyl esters, are provided to students to analyze in order to distinguish between the C-acylation product and the unwanted O-acylation product.

HAZARDS

The starting 3-methyl-1-phenyl-2-pyrazolin-5-one possesses acute oral toxicity and irritates skin and eyes. Calcium hydroxide can cause severe skin irritation, chemical burns, blindness, or lung damage. *p*-Toluoyl chloride is a lachrymator and causes skin and eyes corrosion and burns. Dioxane is a carcinogenic flammable liquid, which is irritating to the eyes and respiratory tract. Exposure may cause damage to the central nervous system, liver and kidneys. Hydrochloric acid is a toxic compound, which has a corrosive effect on human tissue, with the potential to damage respiratory organs, eyes, skin, and intestines irreversibly. The solvents used for TLC and recrystallization, dichloromethane, methanol, ethanol, heptane, and acetone, are flammable liquids. Dichloromethane causes skin and eye irritation and possesses carcinogenicity. Methanol is toxic if swallowed, in contact with skin or if inhaled. Acetone causes serious eye irritation and may cause drowsiness or dizziness. Heptane causes skin irritation and may be fatal if swallowed or inhaled; it is very toxic to aquatic life with long lasting effects. Deuterated chloroform is a suspected carcinogen and should be handled with care. Unprotected exposure to these chemicals has to be limited. Avoid breathing solvent vapors and releasing reagents to the environment.

The hazards of acyl pyrazolones are not known and should be handled with extreme care.

Safety glasses, gloves, and laboratory coat are worn during all exercises. Both syntheses and recrystallizations are carried out by using safety heaters with temperature controllers. All exercises, including NMR sample preparations, are handled in a well-ventilated hood. All wastes are disposed appropriately.

RESULTS

The experiment has been completed one time by eight second-year undergraduate organic chemistry students working in pairs preparing 3-methyl-4-(4-methylbenzoyl)-1-phenyl-pyrazol-5-one in a 50 mmol scale. The crude product was obtained in 87−92% yield and was analyzed by TLC on silica gel. The mobile phase was varied, and it was found that 5% methanol in dichloromethane was the most appropriate solvent system. Three R_f-values were detected in the crude product: R_f 0.55 (desired product), R_f 0.89 (a nonpolar impurity), and R_f 0.43 (a polar impurity).

Recrystallization of the crude product from methanol−acetone afforded pure product in 71−75% yield as colorless plates, mp 126−127 °C; recrystallization from heptane gave yellow needles, mp 102−103 °C. The 1D and 2D NMR spectra were recorded in $CDCl_3$ solutions on a 600 MHz NMR

dx.doi.org/10.1021/ed5000636 | J. Chem. Educ. XXXX, XXX, XXX−XXX

spectrometer. Student spectra and the full assignment of the signals are given in the Supporting Information.

The analyses of the NMR spectra showed that all acyl pyrazolones, 3-methyl-4-(4-methylbenzoyl)-1-phenyl-pyrazol-5-one obtained by the students, and three compounds provided existed in an enol form in chloroform-*d* solution. A comparison with the spectra of the corresponding esters showed that the products contained no ester impurity.

Students' laboratory reports and the results of a questionnaire and exams demonstrated that all pedagogic goals were achieved. Students acquired theoretical and experimental knowledge in the following tasks: (1) what precautions to take during the laboratory exercises depending on the reagents and solvents hazards, (2) how to perform efficiently a three step sequence for selective C-acylation of pyrazolone, (3) how to carry out TLC and analyze the results, (4) how to accomplish the recrystallization from a single solvent and from a solvent system, (5) how to analyze 1D and 2D NMR spectra. All eight second-year undergraduate students acquired sufficient experimental technique and knowledge in NMR spectra interpretation and application in structure determination.

■ CONCLUSIONS

A synthetic approach for the selective C-acylation of pyrazolones was developed and implemented for second-year undergraduate organic chemistry students. The protocol was simple and efficient, and allowed instruction time to be devoted to synthetic, purification, and analytical details. Students acquired basic knowledge in the theory of selective reactions and in the application of NMR spectroscopy in structural analysis.

■ ASSOCIATED CONTENT

Supporting Information

Instructions for the students, notes for instructors, experimental details, spectral and analytical data, pictures of experimental steps and grown crystal phases, NMR spectra. This material is available via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The financial support by the EU Social Fund and Ministry of Education and Science, EU operational program "Development of human resources", project BG051PO001-3.3.07-0002 Student Practices, and by the Bulgarian Science Fund, projects UNA-17/2005 and DRNF-02-13/2009, is gratefully acknowledged. We also thank the eight second-year undergraduate students (S. Angelova, A. Petrova, I. Nikolchina, R. Rusev, A. Jakub, A. Hristova, G. Dimitrova, L. Stoyanova) from the University of Chemical Technology and Metallurgy for reproducing the experiments. The authors are also grateful to FP7-PEOPLE-Marie Curie Actions-IEF for the support of the project INNOVILLN (622906) 2014-2016.

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