Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Improved Pinner Reaction with CPME as a Solvent

Kiyoshi Watanabe [a], Naoto Kogoshi [a], Hideaki Miki [a] & Yasuhiro Torisawa [b]

[a] Specialty Chemicals Division, Zeon Corporation, Tokyo, Japan

[b] Faculty of Pharmacy, Takasaki University of Health and Welfare, Takasaki, Japan

Published online: 27 Apr 2009.

To cite this article: Kiyoshi Watanabe , Naoto Kogoshi , Hideaki Miki & Yasuhiro Torisawa (2009) Improved Pinner Reaction with CPME as a Solvent, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 39:11, 2008-2013, DOI: 10.1080/00397910802632548

To link to this article: http://dx.doi.org/10.1080/00397910802632548

Synthetic Communications®, 39: 2008–2013, 2009

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910802632548

Taylor & Francis
Taylor & Francis Group

Improved Pinner Reaction with CPME as a Solvent

Kiyoshi Watanabe,[1] Naoto Kogoshi,[1] Hideaki Miki,[1] and Yasuhiro Torisawa[2]

[1]Specialty Chemicals Division, Zeon Corporation, Tokyo, Japan
[2]Faculty of Pharmacy, Takasaki University of Health and Welfare, Takasaki, Japan

Abstract: The classical Pinner reaction has been improved by the utilization of 4N-HCl solution in cyclopentyl methyl ether (CPME) as a solvent, wherein direct isolation of the product was possible by a simple filtration.

Keywords: CPME, HCl, Pinner reaction, solvent

INTRODUCTION

Operationally simple synthetic procedures are always in demand for modern process research. Particularly, improvement of classical transformations by replacing hazardous reagents with safer ones that are environmentally benign is an immediate task. The Pinner reaction is a standard process that can combine nitriles with a variety of nucleophiles under anhydrous acidic conditions, affording a useful key intermediate salt for agrochemical and medicinal research. For example, imino ether hydrochlorides (imidates) are useful precursors for the synthesis of heterocyclic ring systems such as oxazoles, imidazoles, and their benzo derivatives. They are also useful in the conversion of nitriles into esters

Received August 13, 2008.
Address correspondence to Yasuhiro Torisawa, Faculty of Pharmacy, Takasaki University of Health and Welfare, 60 Naka Orui, Takasaki, Gunma 370-0033, Japan. E-mail: torisawa@takasaki-u.ac.jp

and for the preparation of amidines, another versatile heterocyclic building block found in various chemicals and pharmaceutics.[1]

Imino ethers are synthesized via the Pinner process in which a nitrile and an alcohol in anhydrous solvent are treated with a large excess of anhydrous hydrogen chloride (HCl) gas. As noted elsewhere, if the reaction is conducted at temperatures warmer than 0°C, the product imino ether salt may decompose to give an amide and an alkyl halide, or in some cases, use of solvent tends to lower the yields of the product. When the nitrile is sterically hindered, the reaction may not take place.[1] Furthermore, the operational drawback associated with this protocol was the use of a large excess of toxic, corrosive, and hard-to-handle HCl gas. It may be difficult to determine exactly how much gas was involved in the reaction mixture, and consequently, a large excess of this hazardous reagent is invariably used, as noted in the patent.[2]

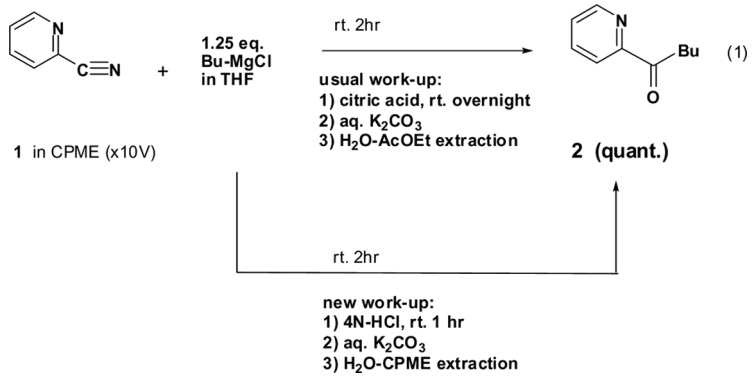
A straightforward improvement might be achieved, however, by the use of HCl solution in a proper solvent. One such improvement has been filed in the recent patent,[2] which now prompted us to disclose our procedure for the improvement of the Pinner process with a new HCl solution, attaining an operationally simple isolation of the resulting imino derivatives in excellent yields.

4N-HCl IN CPME

Our recent review mentioned the invention of the new ethereal solvent, cyclopentyl methyl ether (CPME), as an alternative process solvent, which has show some applicability in modern organic synthesis.[3] Particularly its stability toward HCl and other protic acids including H_2SO_4 is noteworthy. Taking advantage of this nature, a 4N-HCl solution in CPME has been developed and is now available as a commercial product. This stock solution is usually kept in a refrigerator for a long period of time.[3]

We examined the utility of this 4N-HCl solution, first with an application in the workup stage of the conventional Grignard addition to the nitrile **1**. The workup stage of the Grignard reaction needed acidic treatment, and in the case of imine hydrolysis, it often required a long stirring period with aq. citric acid, for example. When 4N-HCl in CPME solution was applied to this hydrolysis, a more convenient and quick workup was attained as shown in Scheme 1.

In particular, in the case of the nitriles without pyridine rings, this workup became more convenient without neutralization of the acidic mixture. CPME was a quite useful ether solvent in the extractive isolation from aqueous acidic mixtures. Such operations are usually small matters in laboratory synthesis, but they are still important in

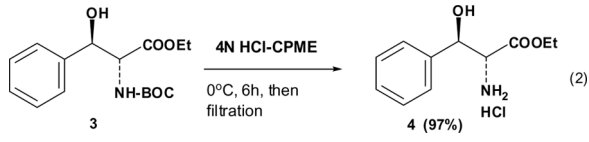


Scheme 1. Workup with 4N-HCl in CPME.

plant work (reduction of workup operations and amounts of solvents employed).

In our second application, further simplification in the workup was demonstrated wherein a simple deprotection of an N-Boc group was attempted in a routine amino acid synthesis as illustrated Scheme 2. Thus, cold 4N-HCl in CPME (4 equiv.) was slowly added to a stirred solution of ethyl (±)-erythro-N-(t-butoxycarbonyl)-2-amino-3-hydroxy-3-phenylpropionate (**3**) in CPME under a nitrogen atmosphere at 0°C. Stirring for 6 h at room temperature completed the deprotection, and the precipitate was collected by filtration, washed with CPME, and dried under vacuum to afford the corresponding 3-phenylserine ethyl ester hydrochloride (**4**)[4] as a white solid (97%). In this way, the deprotection reaction can be carried out by stirring the substrates in 4N-HCl solution followed by simple isolation by filtration to obtain the pure isolated product.

This also indicated that amine hydrochloride salts are usually insoluble in CPME and thus can be easily purified by simple filtration from the reaction mixtures.[3] These applications and other literature precedents[3] indicated we should carry out an improvement of the Pinner process by the use of 4N-HCl in CPME as a key reagent.[3,5]



Scheme 2. Deprotection with 4N-HCl in CPME.

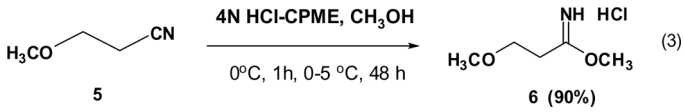
PINNER REACTION IN CPME

Improvement of the Pinner process by 4N-HCl in CPME was carried out, focusing on the safe and effective preparation of some imino ethers from nitrites. Our protocol highlights the fewest operational steps involved for the direct isolation of the pure product. Thus, our protocol for the Pinner reaction in CPME can be exemplified in the following reaction shown in Scheme 2.

Typically, cold 4N-HCl in CPME (4 equiv.) was added to a solution of nitrile and anhydrous methanol (3 equiv.) in CPME ($\times$ 4 V) with stirring under a nitrogen atmosphere at 0°C. The resulting reaction mixture was stirred at 0°C for an additional hour before it was placed in a refrigerator (0–5°C) for 48 h (during this time, white crystalline material precipitated). The precipitate was immediately collected by filtration at room temperature, washed with CPME, and dried under vacuum to afford the crystalline imidate hydrochloride as a white solid (86–91%), which was identical with the authentic material.[2] Our process is very simple and effective with the fewest operational steps when compared with the previous protocol. Extractive workup was tedious and less effective because it took large amounts of extraction solvent, which was evaporated for the isolation of products as shown in the following example with dioxane as a solvent (Scheme 3).

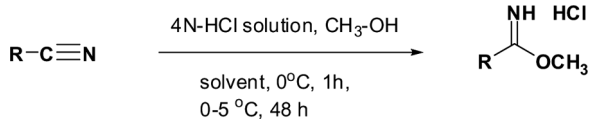
In the previous patent, in which a 4M-HCl solution in dioxane was employed as a solvent for the same transformation, anhydrous ether was required as a cosolvent and tedious workup for the evaporation of dioxane was inevitable before the precipitation of the product with the addition of ether.[2] This protocol thus required ether as an initial solvent, which was evaporated during workup, and further addition of ether for precipitation. Obviously, this is not recommended for scalable preparation of the Pinner products, which are oftentimes sensitive to moisture and very prone to decomposition, as mentioned earlier. The quick workup sequence with CPME solution is thus very valuable in handling such sensitive intermediates. Some other examples are shown in Table 1, demonstrating the ample generality of this protocol.[5]

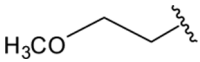
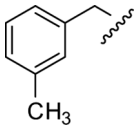
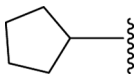
In conclusion, we have demonstrated a very simple Pinner reaction using CPME as the key solvent. In this way, telescoping the lengthy steps



Scheme 3. Pinner reaction with 4N-HCl in CPME.

Table 1. Pinner reaction with 4 N-HCl in CPME



R	HCl solution	Solvent	Yield (%)
	1,4-Dioxane	Et_2O	86[a]
	CPME	CPME	90
	CPME	CPME	86
	CPME	CPME	91

[a]U.S. Patent 6,806,380 B2.[2]

into an operationally simple process is very desirable in modern process research because it reduces the cost of labor and the amount of waste. One of the general strategies for the minimization of the workup stage is a careful selection of the solvent employed, and the present protocol indicates the usefulness of CPME in both the reaction and workup stages. Further application of CPME in process research as well as laboratory synthesis is now in progress. We have surveyed some conventional oxidations, such as Swern oxidation and 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) (radical) oxidation, and these were effectively carried out in CPME as a solvent. Direct chlorination of primary alcohol was possible by stirring 4N-HCl in CPME at ambient temperature. These findings will be reported as subsequent reports in due course.

EXPERIMENTAL

Synthesis of 1,3-Dimethoxypropanimine as a General Procedure

To an ice-cooled and stirred solution of 3-methoxypropionitrile (3, 2.5 g, 29.4 mmol) in anhydrous methanol (3.6 mL, 88.9 mmol) and CPME (10 mL), 4N-HCl solution in CPME (30 mL) was added, and the resulting mixture was kept stirring for 2 h before it was refrigerated for 48 h until

enough white precipitates had formed. The precipitate was immediately collected by filtration at room temperature, washed with CPME (ca. 10 mL), and dried under vacuum to afford the crystalline imidate hydrochloride as a white solid (4, 4.1 g, 91%), identical with the authentic material.[2] ^{1}H NMR ($CDCl_3$): δ 12.72 (br s, 1H), 11.80 (br s, 1H), 4.30 (s, 3H), 3.80 (t, $J = 5.65$ Hz, 2H), 3.25 (s, 3H), 2.95 (t, $J = 5.54$ Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 178.9, 67.7, 61.3, 59.2, 34.0.

The same reaction with 4N-HCl in dioxane was carried out for comparison according to the literature.[2] To an ice-cooled mixture of 3 (29.4 mmol) in anhydrous methanol (88.9 mmol) and ether (10 mL), 4N-HCl solution in dioxane was added, and the resulting mixture was kept stirring for 2 h before it was kept in a refrigerator for 48 h to form a precipitate (during this time, a small amount of white crystalline material precipitated). The reaction mixture was removed from the refrigerator and warmed to approximately 40°C with a warm water bath. Nitrogen gas was then bubbled through the warm reaction mixture to remove excess HCl chloride. The volume of the solvent was further reduced in vacuo, and anhydrous ether (10 mL) was added to effect precipitation. The precipitate was collected by filtration, washed with ether (10 mL), and dried under vacuum to afford 3.9 g (86%) of the authentic crystalline imidate hydrochloride salt (**4**).

ACKNOWLEDGMENT

We thank Drs. Y. Suto and N. Yamagiwa of Takasaki University of Health & Welfare for their helpful assistance in manuscript preparation.

REFERENCES

1. Kürti, L.; Czakó, B. In *Strategic Applications of Named Reactions in Organic Synthesis: Background and Detailed Mechanisms*; Academic Press: San Diego, CA, 2005.
2. Kolb, H. C.; Kanamarlapudi, R. C.; Richardson, P. F.; Khan, G. Modified safe and efficient process for the environmentally friendly synthesis of imidoesters. US Patent 6,806,380 B2, 2004.
3. Watanabe, K.; Yamagiwa, N.; Torisawa, Y. CMPE as an alternative process solvent. *Org. Process Res. Dev.* **2007**, *11*, 251.
4. Hoenig, H.; Seufer-Wasserthal, P.; Weber, H. Chemo-enzymatic synthesis of all isomeric phenylserines and -isoserines. *Tetrahedron* **1990**, *46*, 3841.
5. Kogoshi, N.; Miki, H. Process for producing imidoesters hydrochlorides. JP 2007-320854, 2007.