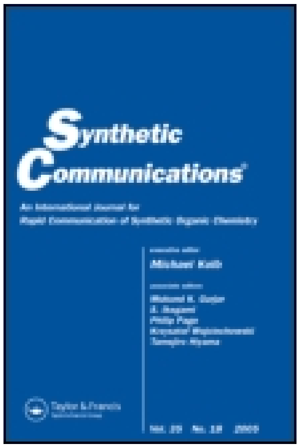
This article was downloaded by: [University of Stellenbosch]
On: 21 July 2013, At: 21:02
Publisher: Taylor & Francis
Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



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

UNEXPECTED REACTION USING METHANOL DRIED OVER MOLECULAR SIEVES

Mamoru Mizuno [a] , Katsuaki Kobayashi [a] , Hitoshi Nakajima [a] , Masahiko Koya [a] & Toshiyuki Inazu [b]
[a] The Noguchi Institute, 1-8-1, Kaga, Itabashi-ku, Tokyo, 173-0003, Japan
[b] The Noguchi Institute, 1-8-1, Kaga, Itabashi-ku, Tokyo, 173-0003, Japan

Published online: 16 Aug 2006.

To cite this article: Mamoru Mizuno , Katsuaki Kobayashi , Hitoshi Nakajima , Masahiko Koya & Toshiyuki Inazu (2002) UNEXPECTED REACTION USING METHANOL DRIED OVER MOLECULAR SIEVES, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 32:11, 1665-1670, DOI: 10.1081/SCC-120004262

To link to this article: http://dx.doi.org/10.1081/SCC-120004262

PLEASE SCROLL DOWN FOR ARTICLE

Taylor & Francis makes every effort to ensure the accuracy of all the information (the “Content”) contained in the publications on our platform. However, Taylor & Francis, our agents, and our licensors make no representations or warranties whatsoever as to the accuracy, completeness, or suitability for any purpose of the Content. Any opinions and views expressed in this publication are the opinions and views of the authors, and are not the views of or endorsed by Taylor & Francis. The accuracy of the Content should not be relied upon and should be independently verified with primary sources of information. Taylor and Francis shall not be liable for any losses, actions, claims, proceedings, demands, costs, expenses, damages, and other liabilities whatsoever or howsoever caused arising directly or indirectly in connection with, in relation to or arising out of the use of the Content.

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden. Terms & Conditions of access and use can be found at http://www.tandfonline.com/page/terms-and-conditions

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

©2002 Marcel Dekker, Inc. All rights reserved. This material may not be used or reproduced in any form without the express written permission of Marcel Dekker, Inc.

SYNTHETIC COMMUNICATIONS, 32(11), 1665–1670 (2002)

Downloaded by [University of Stellenbosch] at 21:02 21 July 2013

UNEXPECTED REACTION USING METHANOL DRIED OVER MOLECULAR SIEVES

Mamoru Mizuno,* Katsuaki Kobayashi, Hitoshi Nakajima, Masahiko Koya, and Toshiyuki Inazu*

The Noguchi Institute, 1-8-1, Kaga,
Itabashi-ku, Tokyo 173-0003, Japan

ABSTRACT

The absolute methanol dried over 3A molecular sieves cleaves the *O*-acetyl group due to the existence of methoxy species generated by the 3A molecular sieves.

Molecular sieves are artificial zeolites consisting of the alkaline or alkaline earth metal salt of aluminasilicate, and its pore size depends on the metal ion. In organic synthesis, molecular sieves have been used as promoters or catalysts. For instance, Y-type molecular sieves have dual functions as Lewis acid and Lewis base, and the synthesis of benzyl decyl ether from 1-decanol and benzyl chloride using K^+-exchanged Y-type molecular sieves as a catalyst has been reported.[1]

Furthermore, molecular sieves are used as drying reagents for organic solvents. For example, the sodium salt of the A-type molecular sieves is called 4A and is used for dichloromethane and acetonitrile, DMF, etc.,

---

*Corresponding authors.

Copyright © 2002 by Marcel Dekker, Inc. www.dekker.com

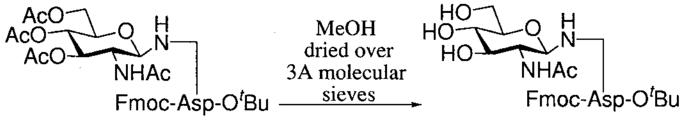
©2002 Marcel Dekker, Inc. All rights reserved. This material may not be used or reproduced in any form without the express written permission of Marcel Dekker, Inc.

Downloaded by [University of Stellenbosch] at 21:02 21 July 2013

the potassium salt is 3A and for methanol and ethanol, and the calcium salt is 5A.

During the preparation of Fmoc-Asn(GlcNAc)-O^{t}Bu as a building block of *N*-glycopeptide,[2,3] we performed the deprotection of the *O*-acetyl group of Fmoc-Asn(GlcNAc(OAc)$_3$)-O^{t}Bu (**1**) in "dry methanol" that was distilled by a conventional method and stored over 3A molecular sieves. In this reaction, surprisingly, cleavage of the *O*-acetyl groups occurred by only dissolving **1** in "dry methanol" without the addition of a reagent[4] (e.g., sodium methoxide) (Scheme 1).

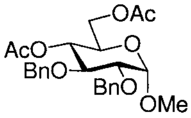
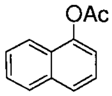
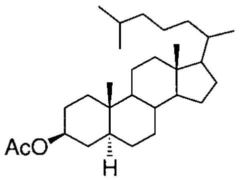
At first, we assumed that the glycosylasparagine derivative **1** was the active species of the methoxy anion, so various *O*-acetyl protected compounds were performed in "dry methanol", however, deacetylation quantitatively proceeded in every case (Table 1).



1

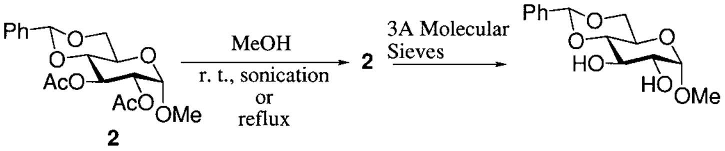
Scheme 1.

Table 1. Deacetylation in Methanol Dried over 3A Molecular Sieves

Substrate	Condition
	Sonication, r.t., 1 h
	Sonication, r.t., 1 h
	Reflux, 12 h

©2002 Marcel Dekker, Inc. All rights reserved. This material may not be used or reproduced in any form without the express written permission of Marcel Dekker, Inc.

Downloaded by [University of Stellenbosch] at 21:02 21 July 2013



Scheme 2.

From this result, we assumed that molecular sieves are the active species of the methoxy anion in methanol. To prove our assumption, the *O*-acetylated compound **2** was dissolved in methanol that was not dried over the 3A molecular sieves and stirred at room temperature with sonication or under reflux conditions. In each case, cleavage of the *O*-acetyl group was not observed at all. 3A molecular sieves were then added to these methanol solutions, and deacetylation proceeded in both cases (Scheme 2). However, we had a suspicion that only our 3A molecular sieves were of low quality, so various 3A molecular sieves from various manufacturers were checked. It was found that all the 3A molecular sieves 3A caused cleavage of the *O*-acetyl group.

From this result, it was clear that the 3A molecular sieves were the active species of the methoxy anion in methanol.[5] Additionally, methanol dried over 4A and 5A molecular sieves were checked for the same deacetylation, and it was found that the 4A molecular sieves were active species of the methoxy anion and not the 5A. However, the 4A molecular sieves and 5A are not used as a drying reagent for methanol due to their pore size, therefore, we focused on the 3A molecular sieves.

After concentration of the methanol dried over the 3A molecular sieves, we found a slightly brown solid as a residue. This slightly brown solid seemed to be insoluble small pieces of molecular sieves. In order to remove this insoluble material, this dry methanol was filtered through a membrane filter ($\phi = 0.45\,\mu m$), however, a slightly brown solid was obtained again after concentration. From this result, we thought that the obtained solid is not molecular sieves but the true active species of the methoxy anion. In fact, the methanol solution of the obtained residue was able to cleave the *O*-acetyl groups.

The amount of soluble matter in the methanol from the 3A molecular sieves is shown in Table 2.[6] On average, about 30 mg of the residue was eluted from the pellet-shaped 3A molecular sieves into the methanol.

The residue was analyzed by X-ray diffraction and electron microprobe analysis, and it was found that the residue did not have the crystal structure of the zeolite any longer and its component was almost totally the

©2002 Marcel Dekker, Inc. All rights reserved. This material may not be used or reproduced in any form without the express written permission of Marcel Dekker, Inc.

Downloaded by [University of Stellenbosch] at 21:02 21 July 2013

Table 2. Residue Amount Released from the 3A Molecular Sieves into the Methanol

Manufacture	Molecular Sieve (Shape)	Residue Amount (mg)
Nacalai	3A 1/8 (pellet)	33
	4A 1/16 (pellet)	5
	3A (powder)	11
Wako	3A 1/8 (pellet)	26
Junsei	3A 1/8 (pellet)	32
Merck	0.3 nm (beads)	10
Nishio	3A 1/8 (pellet)	60

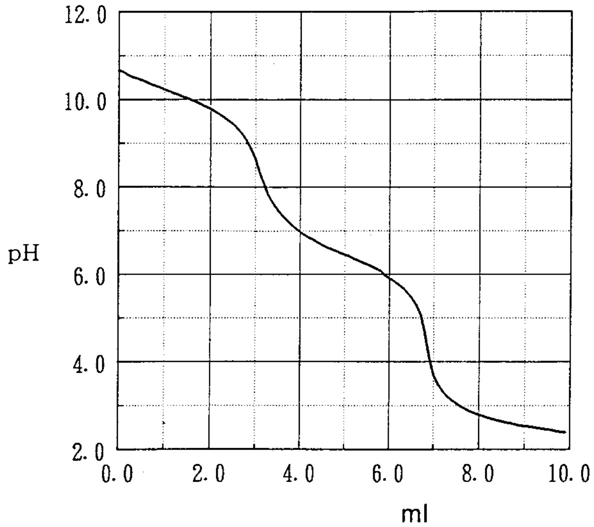


Figure 1. Titration of 0.1 M hydrochloric acid to the aqueous solution of the residue eluted from the 3A molecular sieves.[7]

potassium salt. Furthermore, the neutralization titration curve was very similar to the curve of K_2CO_3 (Figure 1).

Two hypotheses that potassium salt was eluted were as follows: (1) It is well known that zeolites have ion-exchange ability. We assumed that the proton of MeOH was exchanged by K^+ of 3A molecular sieves, and K_2CO_3 resulted from the combination of eluted K^+ and CO_2 from the atmosphere during the preparation of the residue. (2) In the preparation of 3A molecular

©2002 Marcel Dekker, Inc. All rights reserved. This material may not be used or reproduced in any form without the express written permission of Marcel Dekker, Inc.

Downloaded by [University of Stellenbosch] at 21:02 21 July 2013

sieves, Na^+ of Na-type zeolite-A was exchanged to K^+ by KOH, and then the resulting zeolite was washed and heated to dry. At this heating process, KOH, which was not removed by the washing process, converted to K_2O, an absorbed CO_2 in the atmosphere and changed to K_2CO_3. This K_2CO_3, which is impurity in 3A molecular sieves, was eluted into methanol and served as a methoxy species.

We checked acid-washed types of molecular sieves (AW-300)[8] and found that no residue was obtained after concentration of the methanol stored over these sieves. Furthermore the amount of residue eluted from 3A molecular sieves was depended on its manufacture or its shape (Table 2). From these results, the later hypothesis was supported as the major origin of methoxy species.

In conclusion, the 3A molecular sieves release methoxy species in methanol and cleavage of the *O*-acetyl group was caused. If an acid catalyst is used in methanol dried over the 3A molecular sieves, the reaction does not proceed well.[9] To avoid this undesirable reaction, the use of ‘‘normal’’ molecular sieves for methanol is not recommended while using acid-wash type molecular sieves is recommended.

GENERAL PROCEDURE

O-acetylated compound (0.15 mmol) was dissolved in methanol (10 ml) that was dried over 3A molecular sieves for over 24 h. The reaction mixture was sonicated at room temperature, or refluxed until the starting acetate was not observed on TLC. EtOAc was added to the mixture, and the organic layer was washed with water and brine, and dried over Na_2SO_4. After concentration of the organic layer, the crude product was purified by preparative silica gel TLC to give the corresponding de-*O*-acetylated compound.

REFERENCES

1. Izumi, Y.; Urabe, K.; Onaka, M. *Zeolite, Clay, and Heteropoly Acid in Organic Reactions*; Kodansha Ltd.: Tokyo. 1992, pp. 2–21.
2. Inazu, T.; Kobayashi, K. Synlett **1993**, 869.
3. Mizuno, M.; Muramoto, I.; Kobayashi, K.; Yaginuma, H.; Inazu, T. Synthesis **1999**, 162.
4. Greene, T.W.; Wuts, P.G.M. *Protective Groups in Organic Synthesis*, 3rd Ed.; Wiley: New York, 1999; pp. 150–157.

©2002 Marcel Dekker, Inc. All rights reserved. This material may not be used or reproduced in any form without the express written permission of Marcel Dekker, Inc.

5. It was observed that ethanol dried over 3A molecular sieves also cleaved the *O*-acetyl groups, however, the reaction was slower than in methanol.
6. 3A molecular sieves (10 g) were added to methanol (100 ml) and left for 18 h at room temperature. After filtration on a membrane filter ($\phi = 0.45\,\mu\text{m}$), the filtered methanol was concentrated to obtain the resulting residue.
7. 200 g of 3A molecular sieves was dissolved in 30 ml of water.
8. The acid-washed type molecular sieve AW-300 was purchased from Aldrich.
9. We observed that the methylesterification of *N*-acetylneuramic acid in the methanol dried over 3A molecular sieves using an acid catalyst did not proceed well.[10]
10. Kuhn, R.; Lutz, P.; MacDonald, D.L. Chem. Ber. **1966**, *99*, 611.

Received in Japan March 30, 2001

Downloaded by [University of Stellenbosch] at 21:02 21 July 2013