

HETEROCYCLES, Vol. 61, 2003, pp. 97 - 100

Received, 29th August, 2003, Accepted, 8th October, 2003, Published online, 20th October, 2003

MONTMORILLONITE IMPREGNATED WITH BISMUTH NITRATE: MICROWAVE-ASSISTED FACILE NITRATION OF β -LACTAMS[†]

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[†]On the occasion of the 30th Anniversary of Heterocycles, Volume 61

Abstract - A facile synthesis of nitro substituted β -lactams over montmorillonite impregnated with bismuth nitrate under microwave irradiation has been accomplished in excellent yield.

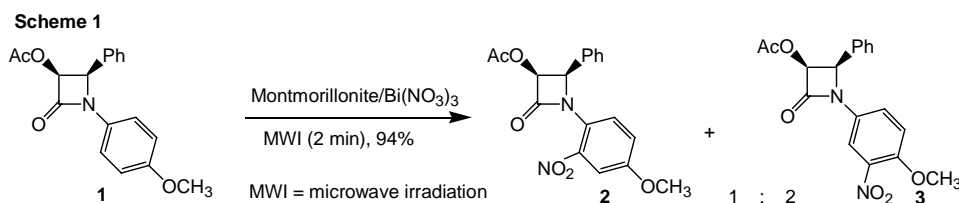
Surface-mediated organic reactions are currently being extensively investigated because they are ecologically friendly.¹ Specifically, a large number of studies of clay-mediated organic reactions have been documented.² We became interested in exploring the use of trivalent bismuth nitrate as the nitrating agent based on our own work with bismuth salts.³ These experiments resulted in a facile synthetic method of nitration of aromatic hydrocarbons and steroids by bismuth nitrate supported on montmorillonite.⁴ We report here the results of our study of bismuth nitrate-mediated synthesis of several nitro β -lactams under microwave irradiation. This method, in principle, can provide 3, 4-*cis* and *trans* nitro substituted β -lactams. Synthesis of these β -lactams using conventional mixed acids is not possible because of the instability of these systems under the conditions described.

We have been engaged in the development of aromatic compounds as antitumor agents.⁵ Nitric acid-sulfuric acid or nitronium tetrafluoroborate was used for synthesis of the nitro compounds. We later discovered that bismuth nitrate on clay is a good reagent for nitration of the substrates.⁴ To avoid complications and the hazards associated with the mixed acid-mediated nitration reaction, nitrating ability of bismuth nitrate was tested to develop simple synthesis of the nitro β -lactams. It has been established that a hydroxy β -lactams on a coupling reaction with baccatin produce taxol and taxotere.⁶ However, no structure-activity studies of taxol and taxotere with an *N*-aryl nitro group (or derivatives thereof) at the C13 side chain has been performed. Therefore, this type of nitro β -lactam (3, 4-*cis* and *trans*) if it is

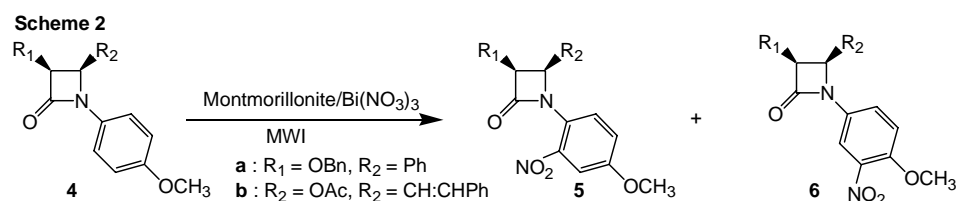
available through this method, can be used for semi synthesis of anticancer taxoid derivatives.

Claycop (montmorillonite clay impregnated with anhydrous cupric nitrate) was used for aromatic nitration reactions.⁷ A large amount of acetic anhydride was required when claycop was used as the nitrating agent and the nitrating species was acetyl nitrate. Also, clayfen with ferric nitrate was used as the reagent for nitration of estrone.⁸ Extreme precautions were necessary in preparing this solid-supported reagent.⁹ Sulfuric acid supported on silica gel was used for the aromatic nitration.¹⁰

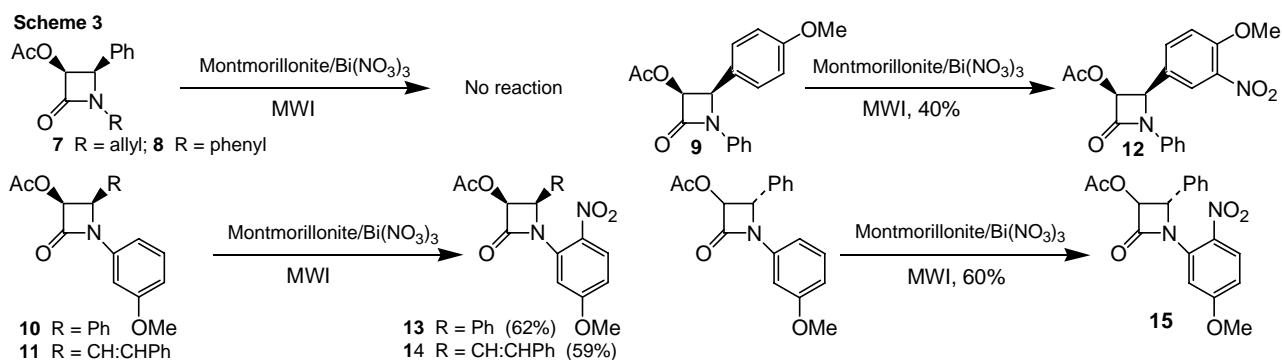
In comparison with the studies described above, the conditions of our bismuth nitrate-mediated reaction were simpler. In particular, mixing the starting *cis* β -lactam (**1**) with bismuth nitrate and montmorillonite in tetrahydrofuran and evaporation of the solvent using a rotavapor afforded nitro β -lactams (**2**) and (**3**) in poor yield. This reaction was not complete, however, brief exposure of microwave irradiation¹¹ to the solid mass helped increase the yield of the products (94%). The structure of products (**2**) and (**3**) was determined from the NMR spectra. Only the aromatic group with the methoxy group was attacked. Cleavage of the β -lactam ring, oxidation of the aromatic system, and deprotection of the ester group were not observed^{4b} (**Scheme 1**).



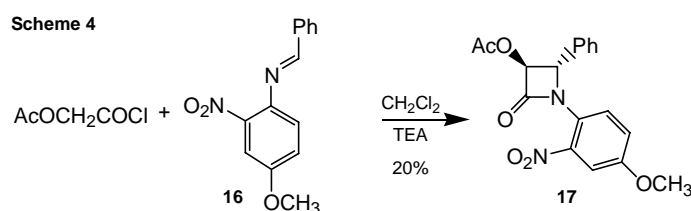
This method was extended to different substrates. For example, *cis* β -lactams containing a benzyloxy group at C3 (**4a**) and styryl group at C4 (**4b**) reacted smoothly with this reagent system and produced products (**5**) and (**6**) (1:2) under microwave irradiation (**Scheme 2**). However, the compounds that had no *p*-methoxy groups (**7** and **8**) remained unaffected under these conditions. On the other hand, it was encouraging to observe nitration of a β -lactam (**9**) having a *p*-methoxyphenyl group at C4. Interestingly, a single nitro β -lactam (**12**) was isolated from this reaction. Changing the location of the methoxy group in the *N*-aryl system influenced the reactivity of the system. The isolated product was a single β -lactam (**13**, **14**, and **15**) when *N*-3-methoxyphenyl-substituted β -lactams (**10**, **11**, and **12**) were used as the starting material. Only the position *para* to the methoxy group was attacked (**Scheme 3**).



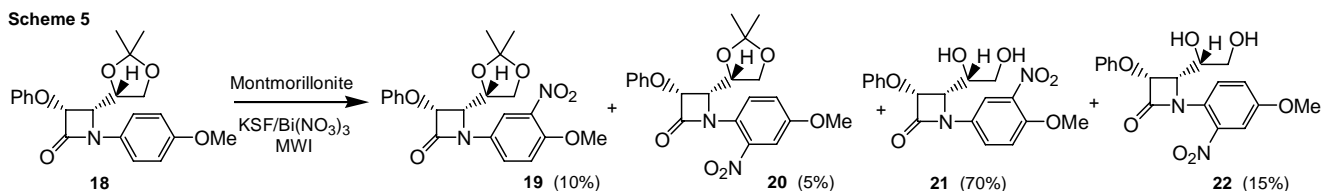
Direct synthesis of a nitro-substituted β -lactam *via* an acid chloride-imine (**16**) cyclization reaction produced *trans* β -lactam (**17**) in low yield without microwave irradiation (**Scheme 4**). Because



annulation with nitroimine (**16**) afforded *trans*- β -lactam (**17**), this bismuth nitrate reaction method is of considerable value for the synthesis of *cis*-substituted nitro β -lactams (for example, **5**, **6**, **12**, **13**, and **14**).



Exploration of our nitration method with a chiral compound (**18**) having *cis* stereochemistry resulted in a mixture of compounds. β -Lactams (**19** and **20**) and diol β -lactams (**21** and **22**) with a nitro group in the *N*-aryl system were obtained. The major products (more than 80%) were **21** and **22** (**Scheme 5**).



Synthesis of the β -lactams substituted with the nitro group in the aromatic systems reported herein would not have been possible without the effects of microwave irradiation. The benefits of microwave irradiation and acceleration of reaction rates in various types of reactions has been the subject of many publications.¹¹ The present study also demonstrates a unique role for microwave irradiation in chemical reactions. Surprisingly, the reaction of β -lactam with bismuth nitrate in refluxing THF generated the product at a very low yield (10%). Therefore, the combination of specific solid support¹² and microwave irradiation was responsible for the success of this reaction.

In summary, this method does not require strong acid¹³ or acetic anhydride, can be applied to a wide range of stereodefined β -lactams (without bond cleavage), and results in a high overall yield.¹⁴ The intermediates^{5b, 6b, 11, 14, 21 and 22} can be modified *via* an oxidation reaction to aldehydes. Based on our previous work on reductive cyclization,¹⁵ it is conceivable that synthesis of multicyclic heterocyclic compounds is highly feasible.

ACKNOWLEDGEMENTS

We gratefully acknowledge the funding support received of this research from M. D. Anderson Cancer Center and NIH Cancer Center Support Grant, 5-P30-CA16672-25, in particular, the shared resources of the Pharmacology and Analytic Center Facility.

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