JOURNAL OF combinatorial CHEMISTRY

Subscriber access provided by American Chemical Society

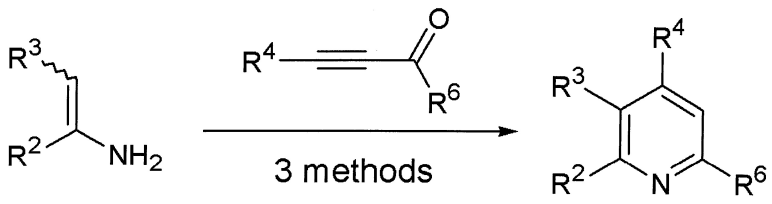
Article

A Facile Solution Phase Combinatorial Synthesis of Tetrasubstituted Pyridines Using the Bohlmann-Rahtz Heteroannulation Reaction

Mark C. Bagley, James W. Dale, Maren Ohnesorge, Xin Xiong, and Justin Bower

J. Comb. Chem., **2003**, 5 (1), 41-44• DOI: 10.1021/cc020067d • Publication Date (Web): 23 November 2002

Downloaded from http://pubs.acs.org on March 20, 2009



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

ACS Publications
High quality. High impact.

Journal of Combinatorial Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

A Facile Solution Phase Combinatorial Synthesis of Tetrasubstituted Pyridines Using the Bohlmann-Rahtz Heteroannulation Reaction

Mark C. Bagley,*,† James W. Dale,† Maren Ohnesorge,† Xin Xiong,† and Justin Bower‡

Department of Chemistry, Cardiff University, P.O. Box 912, Cardiff, CF10 3TB, United Kingdom, and RiboTargets Ltd., Granta Park, Abington, Cambridge, CB1 6GB, United Kingdom

Received August 16, 2002

The solution phase combinatorial Bohlmann−Rahtz reaction gives highly functionalized pyridine libraries from enamino esters and alkynones in a single synthetic step. Good product ratios and library purities were obtained in reactions catalyzed by zinc(II) bromide, the acid-catalyzed heteroannulation procedure offering considerable improvements over traditional methodology.

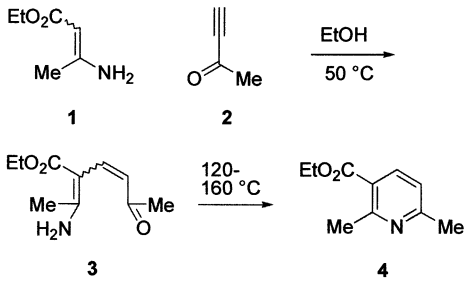
Introduction

The development of new methods for the synthesis of heterocyclic compound libraries, both in solution and on solid phase, is an ever-expanding area in combinatorial chemistry. The pyridine structural motif may be found in a large number of pharmaceutical agents with a diverse range of biological properties,[1] as a pharmacophore of considerable historical importance. Although there is a wide range of methods available for the synthesis of pyridines, very few of these procedures have been developed in combinatorial chemistry[2] and there is a great need for new simple and facile procedures that can incorporate a number of points of structural diversity and a variety of substitution patterns in the target pyridine library.

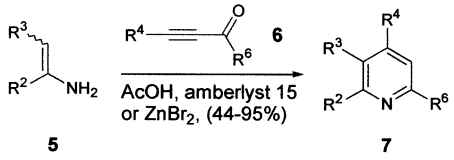
The Bohlmann−Rahtz synthesis of pyridine **4** is a two step process, involving the Michael addition and subsequent cyclization of ethyl β-aminocrotonate **1** and but-3-yn-2-one **2**, first reported in 1957.[3] This little-used heteroannulation reaction proceeds via aminoheptadienone intermediate **3**, which is isolated and heated to high temperature to facilitate cyclodehydration (Scheme 1). Since its discovery, very few applications of this reaction have appeared in the literature, in the total synthesis of the natural product promothiocin A,[4] a member of the thiopeptide class of antibiotics,[5] and in the synthesis of novel heterocyclic substituted α-amino acids.[6]

To improve the scope and versatility of this reaction, we established a new one step method, using either acetic acid or amberlyst 15 ion exchange resin, for the synthesis of trisubstituted (R^4═H) or tetrasubstituted pyridine **7** from enamine **5** and alkynone **6** that avoided the use of high cyclodehydration temperatures (Scheme 2).[7] Furthermore, by using zinc(II) bromide as a Lewis acid catalyst for this reaction,[8] we demonstrated that a single one step procedure was successful for a whole range of different enamines.[9]

Scheme 1. Bohlmann−Rahtz Heteroannulation Reaction.



Scheme 2. One Step Synthesis of Tetrasubstituted Pyridine **7**.



In this paper, we report on the use of the Bohlmann−Rahtz heteroannulation reaction for the combinatorial synthesis of tri- and tetrasubstituted pyridines. The traditional two step method has been compared with both of our one step experimental procedures using a number of different enamines and alkynones to establish the best procedure and optimum conditions for generating pyridine libraries. Furthermore, this study expands the scope of this little-used and yet extremely facile heteroannulation method and highlights how different experimental conditions can have a large influence on product distributions in combinatorial chemistry. This approach has the potential to access highly substituted and heavily functionalized pyridines directly from readily available starting materials without any need for subsequent purification and so should complement other published procedures for the solution phase combinatorial synthesis of pyridine libraries.

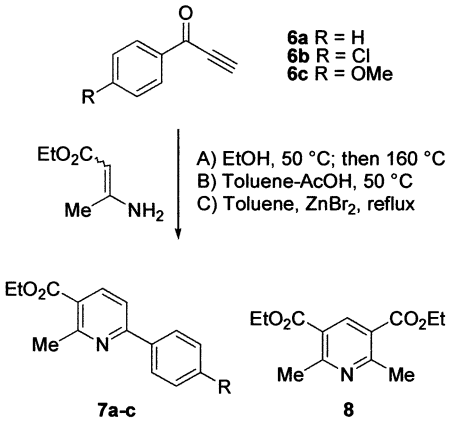
Results and Discussion

To examine the behavior of the different Bohlmann−Rahtz heteroannulation methods, including the traditional method

* To whom correspondence should be addressed. Fax: +44(0)29 2087 4030. E-mail: bagleymc@cf.ac.uk.
† Cardiff University.
‡ RiboTargets Ltd..

10.1021/cc020067d CCC: $25.00 © 2003 American Chemical Society
Published on Web 11/23/2002

Scheme 3. Bohlmann−Rahtz Heteroannulation Reactions for the Synthesis of Pyridines **7a**−**c**.



and the procedures developed in our laboratories,[9] for the solution phase combinatorial synthesis of pyridine libraries, ethyl β-aminocrotonate was reacted with a mixture of three alkynones (Scheme 3). These alkynones were predicted to have different reactivities in this process, and so, this study would provide a valuable comparison between the available procedures. In three separate combinatorial reactions, ethyl β-aminocrotonate was reacted with a mixture of 1-phenylprop-2-yn-1-one **6a**, 1-(4-chloro)phenylprop-2-yn-1-one **6b**, and 1-(4-methoxy)phenylprop-2-yn-1-one **6c** using either traditional Bohlmann−Rahtz conditions (method A), stirring in acetic acid−toluene (method B), or the Lewis acid-catalyzed heteroannulation process (method C).

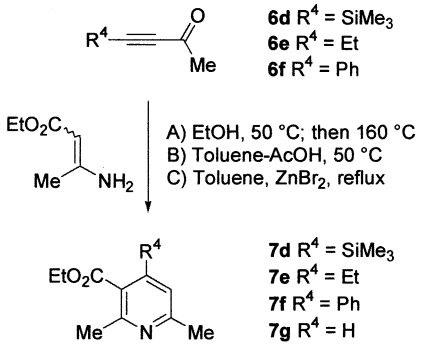
The pyridine products **7** were isolated following an acid−base workup, which was found to be superior to the use of an acidic cation exchange resin (DOWEX 50 W X 8)[2] for these compounds. Analysis by ^{1}H NMR spectroscopy and comparison to the spectra of the pure pyridines isolated in previous studies[9] determined the product ratios by integration of pyridine 4-H or 5-H resonances and library purity by reference to a known quantity of tetramethylsilane as an internal standard according to established methodology (this method of purity determination was further validated by integration of all impurities and, in all cases, was found to be reliable).[2]

In comparing the heteroannulation procedures, the traditional Bohlmann−Rahtz reaction (method A) resulted in the formation of pyridines **7a**−**c**, although it was alkynone **6b** that seemed to behave poorly in the heteroannulation reaction leading to a product ratio (R) that varied between $1 < R < 3.7$. Using acid-catalyzed conditions, the overall yield was lowered and product ratios increased although in the zinc(II) bromide-catalyzed heteroannulation reaction a very high library purity was obtained. Curiously, these reactions also gave rise to a new pyridine product **8**, hitherto unseen in the Bohlmann−Rahtz heteroannulation reaction, and identified by ^{1}H and ^{13}C NMR spectroscopic analysis, high- and low-resolution mass spectrometry, and comparison of characterization data with literature studies. Although surprising, this did serve to increase the diversity of the pyridine library and must have been generated by the hitherto unreported degradation of ethyl β-aminocrotonate under the reaction conditions (Table 1).

Table 1. Comparison of Bohlmann−Rahtz Reaction for the Combinatorial Synthesis of Pyridine **7**

method	products	overall yield (%)	ratio	library purity (%)
A	**7a**−**c**	53	89:27:100	78
B	**7a**−**c**, **8**	43	89:10:100:5	74
C	**7a**−**c**, **8**	38	92:17:100:28	94

Scheme 4. Combinatorial Synthesis of Pyridines **7d**−**g**.



In previous heteroannulation reactions using a number of different readily available starting materials, we have reported that the reaction course and yield often vary according to the structure of the alkynone,[7,9] presumably as a consequence of differences in reactivity. Thus, in developing a combinatorial approach, overcoming these complications and establishing a method that gave rise to pyridine product ratios that reflected the ratio of alkynone starting materials were our principal goals. To this end, an excess of ethyl β-aminocrotonate was reacted with an equimolar mixture of three problematic but-3-yn-2-ones **6d**−**f**, which varied in the nature of the 4-substituent and that have been reported to react differently in heteroannulation processes (Scheme 4).[7,9]

A small library of pyridines **7d**−**g** was generated using each of the three methods A−C, isolated as before and analyzed by ^{1}H NMR spectroscopic methods to establish the overall yield, purity, and product distribution. It was observed that this set of alkynones gave rise to a slightly larger range of product ratios (R) although in all cases pyridine **7** was formed. Using the traditional two step procedure (method A), heating the mixture to 50 °C in ethanol, isolating the intermediate, and then heating to 160 °C for 3 h to affect cyclodehydration resulted in the isolation of four pyridines **7d**−**g**, with desilylation occurring throughout the course of reaction. With this in mind, product ratios were large and varied between $1 < R < 25$, although the overall yield and product purity were good. Some desilylation also accompanied the reaction conducted in toluene−acetic acid (method B) and although the product ratio (R) improved, varying between $1 < R < 8.3$, the overall yield was low (30%). However, the Lewis acid-catalyzed conditions (method C) resulted in no desilylation and thus gave rise to only three pyridines **7d**−**f** in high purity, good overall yield, and in a product ratio (R) that only varied between $1 < R < 2$. Repeating this reaction but with a reduction in the molar equivalents of ethyl β-aminocrotonate (method C) did not seem to affect the overall yield or library purity but improved the product ratio (R), which varied between $1 < R < 1.6$. It was curious to note that the product ratio varied between

Scheme 5. Bohlmann−Rahtz Heteroannulation for the Combinatorial Synthesis of Tetrasubstituted Pyridines.

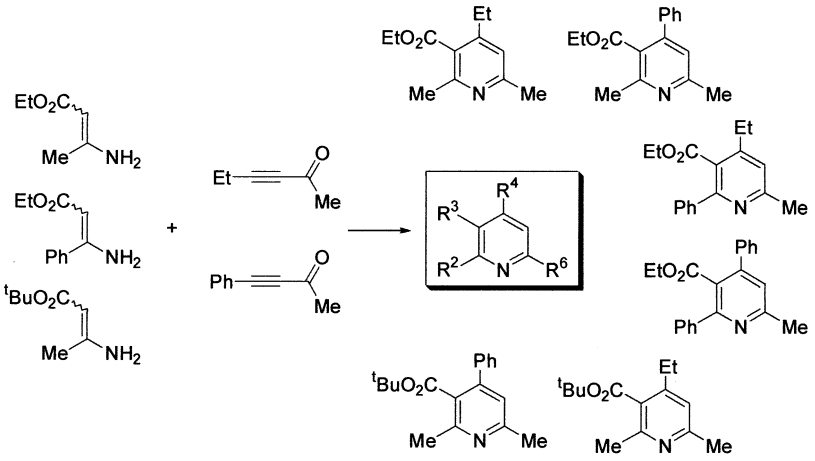


Table 2. Comparison of Bohlmann−Rahtz Heteroannulation Procedures for the Combinatorial Synthesis of Pyridine **7d−g**

method	products	yield (%)	ratio	library purity (%)
A	**7d−g**	62	100:65:4:54	75
B	**7d−g**	30	52:100:67:12	80
C	**7d−f**	64	100:73:50	86
C[a]	**7d−f**	62	63:100:63	85

[a] Double the number of equivalents of alkynone starting materials were used.

the different heteroannulation procedures, as did the identity of the major product, indicating that the alkynones display different reactivity profiles according to the method used (Table 2).

The Lewis acid-catalyzed methods appeared to provide the best overall yield, product ratios, and library purity for the solution phase combinatorial synthesis of pyridines from ethyl β-aminocrotonate in the Bohlmann−Rahtz reaction. As a final study, it was decided to investigate the Lewis acid-catalyzed procedure using a number of different enamines to examine if tetrasubstituted pyridines could be generated in a combinatorial Bohlmann−Rahtz reaction. Following acid−base extraction, the crude reaction mixture was found to contain all six possible pyridine products by ^{1}H NMR spectroscopic analysis. Although the product ratios were large ($1 < R < 25$), due to the low reactivity of 4-phenylbut-3-yn-2-one (ratios for the pyridines generated from hex-3-yn-2-one varied between $1 < R < 2.6$),[7] the library purity was very high (88% by comparison with tetramethylsilane) and a complete library of products had been generated in 39% overall yield.

Conclusion

The Bohlmann−Rahtz heteroannulation reaction was successful for the combinatorial synthesis of pyridine libraries in solution. In all of the reactions investigated, a complete pyridine library was generated with very low levels of impurities using a simple acid−base extraction workup procedure. Product ratios varied according to the heteroannulation method used and alkynone structure, but even using problematic alkynones with different reactivities, the Lewis acid-catalyzed heteroannulation reaction was successful for the combinatorial synthesis of pyridine libraries in solution.

Experimental Section

General Details. Commercially available reagents were used without further purification; solvents were dried by standard procedures. Unless otherwise stated, reactions were performed under an atmosphere of dry nitrogen. Melting points were determined on a Kofler hot stage apparatus, and they are uncorrected. Infrared spectra were recorded in the range of 4000−600 cm^{-1} on a Perkin-Elmer 1600 series FTIR spectrometer using KBr disks for solid samples and thin films between NaCl plates for liquid samples, and they are reported in cm^{-1}. NMR spectra were recorded using a Bruker DPX 400 instrument operating at 400 MHz for ^{1}H spectra and 100 MHz for ^{13}C spectra; *J* values were recorded in Hz, and multiplicities were expressed by the usual conventions. Low-resolution mass spectra were determined using a Fisons VG Platform II Quadrupole instrument. APcI refers to atmospheric pressure chemical ionization, and EI refers to electron ionization. High-resolution mass spectra were obtained courtesy of the EPSRC Mass Spectrometry Service at University College of Wales, Swansea, U.K., using the ionization methods specified.

Typical Procedure for Two Step Bohlmann−Rahtz Heteroannulation (Method A). A solution of ethyl β-aminocrotonate (0.19 g, 1.5 mmol), 1-phenylprop-2-yn-1-one **6a** (32 mg, 0.25 mmol), 1-(4-chlorophenyl)prop-2-yn-1-one **6b** (41 mg, 0.25 mmol), and 1-(4-methoxyphenyl)prop-2-yn-1-one **6c** (40 mg, 0.25 mmol) in ethanol (12 mL) was stirred at 50 °C for 5 h, cooled, and then evaporated in vacuo. The residue was heated at 160 °C in a sand bath for 2 h, allowed to cool, and partitioned between hydrochloric acid (2 M; 12 mL) and ethyl acetate (16 mL). The aqueous layer was washed successively with ethyl acetate (3 × 16 mL), basified to pH 10 with aqueous sodium hydroxide solution (5 M), and allowed to cool. The mixture was extracted with ethyl acetate (3 × 16 mL), and the organic extracts were combined, washed with brine (15 mL), dried (Na_2SO_4), and evaporated in vacuo to give pyridines **7a−c** and **8** as a pale yellow solid (0.10 g, 53%).

Typical Procedure for Bohlmann−Rahtz Heteroannulation Catalyzed by Acetic Acid (Method B). A solution

of ethyl β-aminocrotonate (0.19 g, 1.5 mmol), 1-phenylprop-2-yn-1-one **6a** (32 mg, 0.25 mmol), 1-(4-chlorophenyl)prop-2-yn-1-one **6b** (41 mg, 0.25 mmol), and 1-(4-methoxyphenyl)-prop-2-yn-1-one **6c** (40 mg, 0.25 mmol) in toluene−glacial acetic acid (5:1) (6 mL) was stirred at 50 °C for 6 h. The mixture was allowed to cool and partitioned between ethyl acetate (12 mL) and saturated aqueous sodium hydrogen carbonate solution (30 mL). The aqueous layer was further extracted with ethyl acetate (12 mL), and the organic layers were combined and extracted with hydrochloric acid (2 M; 2 × 12 mL). The aqueous extracts were combined, washed with ethyl acetate (4 × 15 mL), basified to pH 10 with aqueous sodium hydroxide solution (5 M), and allowed to cool. The mixture was extracted with ethyl acetate (3 × 16 mL), and the organic extracts were combined, washed with brine (15 mL), dried (Na_2SO_4), and evaporated in vacuo to give pyridines **7a**−**c** and **8** as a pale yellow solid (82 mg, 43%).

Typical Procedure for Bohlmann−Rahtz Heteroannulation Catalyzed by Zinc(II) Bromide (Method C). A solution of ethyl β-aminocrotonate (0.19 g, 1.5 mmol), 1-phenylprop-2-yn-1-one **6a** (32 mg, 0.25 mmol), 1-(4-chlorophenyl)prop-2-yn-1-one **6b** (41 mg, 0.25 mmol), and 1-(4-methoxyphenyl)prop-2-yn-1-one **6c** (40 mg, 0.25 mmol) in toluene (10 mL) was heated at reflux in the presence of zinc(II) bromide (25 mg, 15 mol %) for 6 h. Water (5 mL) was added, and the solution was heated at reflux for 15 min, allowed to cool, and partitioned between hydrochloric acid (2 M; 12 mL) and ethyl acetate (16 mL). The aqueous layer was washed successively with ethyl acetate (3 × 16 mL), basified to pH 10 with aqueous sodium hydroxide solution (5 M), and allowed to cool. The mixture was extracted with ethyl acetate (3 × 16 mL), and the organic extracts were combined, washed with brine (15 mL), dried (Na_2SO_4), and evaporated in vacuo to give pyridines **7a**−**c** and **8** as a pale yellow solid (72 mg, 38%).

Yield and Ratio Determination by ^{1}H NMR. The addition of a known quantity of tetramethylsilane was used as an internal standard ($\delta = 0.00$ ppm) for the determination of yields and product ratios. Integration of the 5-H and 4-H signals where relevant, appearing as singlets or doublets, gave the relative ratios of pyridine products. Comparison was made to chromatographically homogeneous samples of pyridines prepared and characterized individually according to our Bohlmann−Rahtz procedures (see Supporting Information).[9]

Acknowledgment. We thank the E.P.S.R.C. (CNA to J.W.D.) and Royal Society for support of this work and the E.P.S.R.C. Mass Spectrometry Service, Swansea, for high-resolution mass spectra.

Supporting Information Available. Experimental procedures for the synthesis of alkynone starting materials **6a**−**c** and characterization data for pyridine **7b**,**c** and **8**, alkynones **6b**,**c**, and other intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Roth, H. J.; Kleemann, A. In *Pharmaceutical Chemistry. Volume 1: Drug Synthesis*; John Wiley & Sons: New York, 1988.
(2) Nettekoven, M. *Synlett* **2001**, 1917. (b) Breitenbucher, J. G.; Figliozzi, G. *Tetrahedron Lett.* **2000**, *41*, 4311. (c) Brändli, C.; Ward, T. R. *J. Comb. Chem.* **2000**, *2*, 42. (d) Bhandari, A.; Li, B.; Gallop, M. A. *Synthesis* **1999**, 1951. (e) Grosche, P.; Höltzel, A.; Walk, T. B.; Trautwein, A. W.; Jung, G. *Synthesis* **1999**, 1961. (f) Chiu, C.; Tang, Z.; Ellingboe, J. W. *J. Comb. Chem.* **1999**, *1*, 73. (g) Lago, M. A.; Nguyen, T. T.; Bhatnagar, P. *Tetrahedron Lett.* **1998**, *39*, 3885. (h) Marzinzik, A. L.; Felder, E. R. *J. Org. Chem.* **1998**, *63*, 723. (i) Gordeev, M. F.; Patel, D. V.; Gordon, E. M. *J. Org. Chem.* **1996**, *61*, 924. (j) Gordeev, M. F.; Patel, D. V.; Wu, J.; Gordon, E. M. *Tetrahedron Lett.* **1996**, *37*, 4643. (k) Powers, D. G.; Casebier, D. S.; Fokas, D.; Ryan, W. J.; Troth, J. R.; Coffen, D. L. *Tetrahedron* **1998**, *54*, 4085.
(3) Bohlmann, F.; Rahtz, D. *Chem. Ber.* **1957**, *90*, 2265.
(4) Moody, C. J.; Bagley, M. C. *Synlett* **1998**, 361.
(5) Bagley, M. C.; Bashford, K. E.; Hesketh, C. L.; Moody, C. J. *J. Am. Chem. Soc.* **2000**, *122*, 3301.
(6) Adlington, R. M.; Baldwin, J. E.; Catterick, D.; Pritchard, G. J.; Tang, L. T. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2311 and references therein.
(7) Bagley, M. C.; Dale, J. W.; Bower, J. *Synlett* **2001**, 1149.
(8) Bagley, M. C.; Dale, J. W.; Hughes, D. D.; Ohnesorge, M.; Phillips, N. G.; Bower, J. *Synlett* **2001**, 1523.
(9) Bagley, M. C.; Brace, C.; Dale, J. W.; Ohnesorge, M.; Phillips, N. G.; Xiong, X.; Bower, J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1663.

CC020067D