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Cycloaddition studies directed toward the strychnos alkaloid minfiensine

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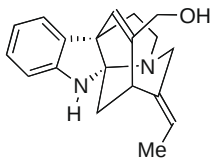
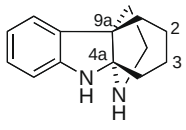
ABSTRACT

The thermolysis of several imidofuranyl carbamates delivers products derived from an intramolecular [4+2]-cycloaddition reaction. In the case of the *ortho*-azido aryl carbamate **13**, the preferred path proceeds by an electrocyclization of a nitrene intermediate to produce a 3-substituted indole. Attempts to reduce the azido group resulted in a novel intramolecular aza-Wittig reaction with the neighboring imido group.

Cascade reactions where the conversion of a starting material to a product that then becomes a substrate for the next reaction are highly desirable not only due to their elegance, but also because of their efficiency and economy in terms of reagent consumption and purification.[1–3] These multistep, one-pot procedures are often accompanied by dramatic increases in molecular complexity.[4–6] For the past several years, our research group has been investigating the intramolecular [4+2]-cycloaddition/rearrangement cascade of 2-amidofurans (IMDAF) as a strategy for the synthesis of hexahydroindolinone alkaloids.[7] Our recently completed syntheses of (±)-erysotramidine,[8] (±)-lycoricidine,[9] and (±)-strychnine[10] nicely demonstrate the utility of this cascade process for the construction of various alkaloids. On the basis of our earlier work, we felt that we could also use this methodology for the synthesis of the strychnos alkaloid minfiensine (**1**). This unusual alkaloid was isolated from the African plant *Strychnos minfiensis* by Massiot and coworkers in 1989, and possesses a highly challenging pentacyclic ring framework.[11] The 1,2,3,4-tetrahydro-9*a*,4*a*-iminoethano-carbazole core (**2**) represents the defining feature of minfiensine and this tetracyclic framework can also be found in a number of related akuammiline alkaloids.[12,13] While two total syntheses of minfienine have already been reported,[14] beginning with Overman's brilliant synthesis in 2005,[15] only a few successful methods to prepare the tetracyclic sub-ring have been described to date.[16]



1; minfiensine



2; 9*a*,4*a*-iminoethano-carbazole

We reasoned that minfiensine (**1**) might be assembled by employing the domino cycloaddition/rearrangement cascade[7] of 2-amidofuran **3** as outlined in Scheme 1. The synthetic plan we had in mind for minfiensine involves generation of the E-ring of ester **7** by a palladium catalyzed intramolecular enolate coupling[17] of the tethered vinyl iodide **6** as was recently carried out in our synthesis of strychnine.[10] We envisioned the formation of **6** as coming about by cyclization of the anilino group (or its equivalent) onto the *N*-acyliminium ion present in **5**, which we intended to generate by the protonation of the *3a*-aryl-2,3,3*a*,4-tetrahydro-1*H*-indol-5(6*H*)-one **4b**. The formation of **4b** should occur by an IMDAF cycloaddition reaction of amidofuran **3b** (X = NH_2) followed by a subsequent rearrangement of the initially formed [4+2]-oxabicyclic adduct.[7] It should be noted that our group had previously reported on the thermal cascade reaction of furanyl carbamate **3a** (X = H), which cleanly afforded cycloadduct **4a** in 85% yield, thereby providing good precedent for the key cycloaddition step in the proposed scheme.[18]

As the goal of our initial efforts, we chose to examine the thermal chemistry of the nitro-aryl substituted carbamate **3c** (X = NO_2) in order to test the proposed methodology. Our intention was to reduce the nitro functionality to the corresponding amino group either in the starting amidofuran (i.e., **3c**→**3b)** or else in the resulting rearranged cycloadduct (i.e., **4c**→**4b**). We were surprised to discover, however, that heating a sample of **3c** at 200 °C for 3 days gave no sign of any product derived from a [4+2]-cycloaddition reaction and only the starting carbamate was recovered. We were able to cleanly reduce **3c** into **3b** using some conditions reported by Heathcock[19] ($Cu(acac)_2$); $NaBH_4$/EtOH). However, as was the case with the nitro system, the thermolysis of **3b** at 200 °C only resulted in recovered starting material. One possible explanation that might account for the lack of reactivity of these systems is that the presence of a substituent group in the ortho position causes an unfavorable steric interaction with the furan ring in the reactive '*Diels–Alder conformation*' thereby diminishing the overall rate of the IMDAF cycloaddition.

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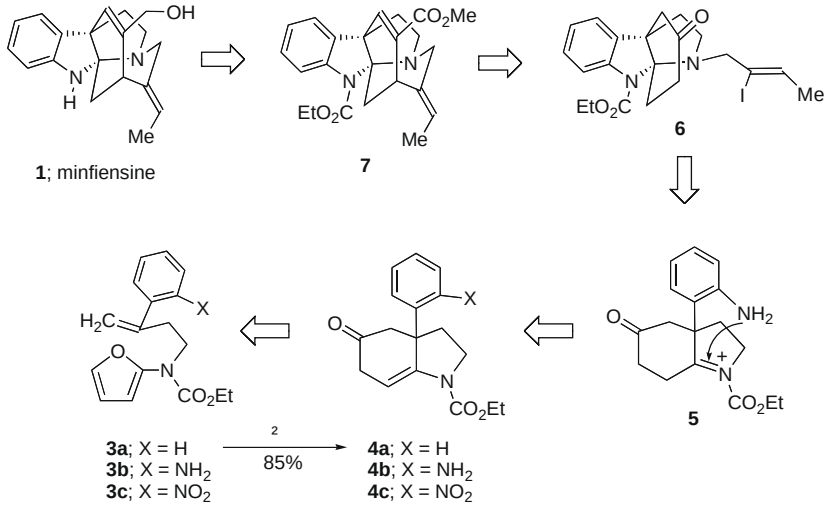


Scheme 1.

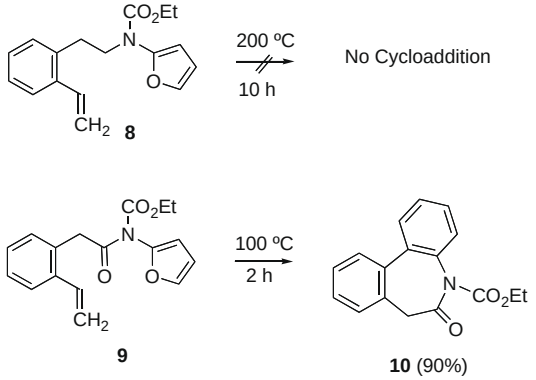
In earlier studies, we had demonstrated that conformation effects can have a dramatic impact on the rate of the IMDAF reaction of amido-substituted furans.[20] Specifically, the incorporation of an imido carbonyl group in the tether that joins the dienophile and furan moieties results in a conformation where the π-bond and the furan ring are in closer proximity, thereby facilitating the cycloaddition reaction relative to the simpler amine system. An example that illustrates this marked rate difference is seen in the thermal chemistry of carbamate **8** versus imidofuran **9**. Heating a sample of **8** at 200 °C for 10 h gave no sign of any product derived from a [4+2]-cycloaddition. In sharp contrast, **9** gave **10** in 90% isolated yield when heated at 100 °C for 2 h. In this case, the initially formed Diels–Alder cycloadduct underwent ring opening and a subsequent loss of water to produce the aromatized product **10** (Scheme 2).

In an attempt to exploit this conformational facilitating effect, we first opted to study the IMDAF reaction of the *o*-bromo substituted imidofuranyl carbamate **11**. We found that the intramolecular cycloaddition behavior of **11** in response to the presence of a C=O group in the tether was striking. Thus, the thermolysis of **11** at 150 °C in toluene afforded 2,5-dioxohexahydro-1*H*-indole **12** in 90% isolated yield (Scheme 3). Unfortunately, all of our efforts to convert the bromo group into an amino functionality using Buchwald/Hartwig amination procedures[21] failed.

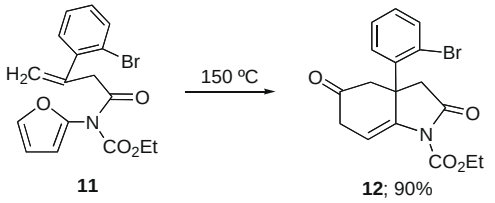
Nevertheless, armed with this promising result, we set out to explore the cycloaddition chemistry of the related *o*-azido furanyl carbamate **13** as we thought that the relatively small and linear azido group could be easily reduced. We found, however, that heating a sample of **13** in refluxing toluene produced only the 3-substituted indole **15** with no signs of an IMDAF cycloadduct being present in the crude reaction mixture. Apparently, loss of nitrogen from azide **13** followed by an electrocyclization[22] to give **14** and then indole **15** by a 1,5-hydrogen shift proceeds at a faster rate than the IMDAF cycloaddition.

To avoid this competitive cyclization problem, we decided to first reduce the azido group to the corresponding amine. A standard method for azide reduction involves its reaction with triphenylphosphine which leads to the formation of the corresponding iminophosphorane (i.e., **16**). In the presence of water, hydrolysis generally occurs quite rapidly to produce the primary amine and triphenylphosphine oxide (Staudinger reduction).[23] However, with the above system, iminophosphorane **16** preferred to react with the adjacent imido carbonyl group in an aza-Wittig manner[24] to deliver dihydroquinoline **17**, which then tautomerized to the more stable quinoline **18** (Scheme 4). Although amides are not traditionally used as the carbonyl coupling partner for intramolecular aza-Wittig reactions, there are a number of reports in the literature describing the use of this reaction for the synthesis of various nitrogen containing heterocycles[24,25].

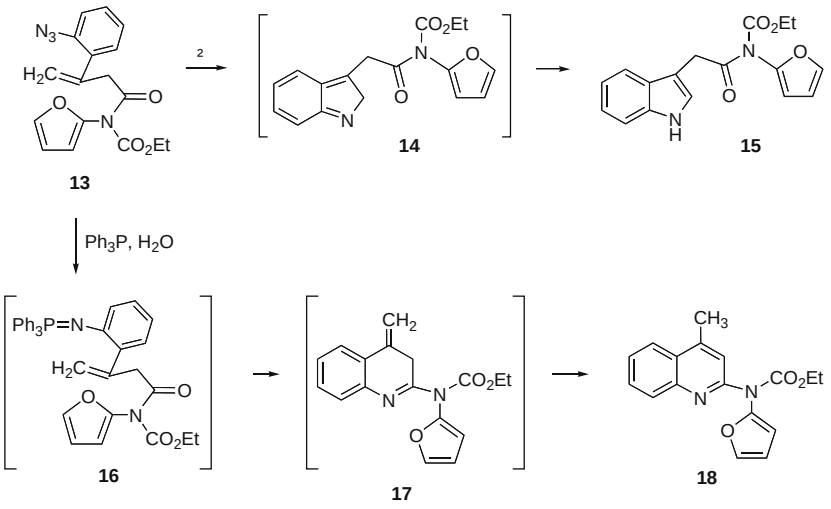
In conclusion, we have tested a strategy for the eventual construction of the 9*a*,4*a*-iminoethano-carbazole framework of minfiensine using the IMDAF rearrangement cascade of 2-imidofurans. Furanyl carbamates with carbonyl groups in the tether provided the desired cycloaddition product. Those lacking the carbonyl group failed to cyclize. We now plan to find an alternate set of conditions to reduce the *o*-azido group of carbamate **13** and explore its conversion to the key 5-oxo-hexahydro-1*H*-indole intermediate. Further progress toward the total synthesis of minfiensine (**1**) is ongoing in this laboratory and will be reported in due time.



Scheme 2.



Scheme 3.



Scheme 4.

Acknowledgments

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References and notes

1. (a) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131; (b) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115.
2. (a) Ho, T. L. *Tandem Organic Reactions*; Wiley: New York, 1992; (b) Bunce, R. A. *Tetrahedron* **1995**, *51*, 13103; (c) Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195.
3. Ziegler, F. E.. In Paquette, L. A., Ed.; Comprehensive Organic Synthesis Combining C–C π-Bonds; Pergamon Press: Oxford, 1991; Vol. 5, Chapter 7.3,.
4. Waldmann, H. In *Domino Reaction in Organic Synthesis Highlight II*; Waldmann, H., Ed.; VCH: Weinheim, 1995; pp 193–202.
5. Curran, D. P.. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, p 779.
6. Wender, P. A., Ed.; Frontiers in Organic Synthesis. *Chem. Rev.* **1996**, *96*, 1–600.
7. (a) Padwa, A.; Dimitroff, M.; Waterson, A. G.; Wu, T. *J. Org. Chem.* **1997**, *62*, 4088; (b) Padwa, A.; Brodney, M. A.; Dimitroff, M. *J. Org. Chem.* **1998**, *63*, 5304; (c) Padwa, A.; Brodney, M. A.; Satake, K.; Straub, C. S. *J. Org. Chem.* **1999**, *64*, 4617.
8. Padwa, A.; Wang, Q. *J. Org. Chem.* **2006**, *71*, 7391.
9. Zhang, H.; Padwa, A. *Org. Lett.* **2006**, *8*, 247.
10. (a) Zhang, H.; Boonsombat, J.; Padwa, A. *Org. Lett.* **2007**, *9*, 279; (b) Boonsombat, J.; Zhang, H.; Chughtai, M. J.; Hartung, J.; Padwa, A. *J. Org. Chem.* **2008**, *73*, 3539.
11. Massiot, G.; Thepenier, P.; Jacquier, M. J.; Le Men-Olivier, L.; Delaude, C. *Heterocycles* **1989**, *29*, 1435.
12. Ramirez, A.; Garcia-Rubio, S. *Curr. Med. Chem.* **2003**, *10*, 1891.
13. Anthoni, U.; Christophersen, C.; Nielson, P. H.. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1999; Vol. 13, pp 163–236.
14. (a) Dounay, A. B.; Humphreys, P. G.; Overman, L. E.; Wrobleski, A. D. *J. Am. Chem. Soc.* **2008**, *130*, 5368; (b) Shen, L.; Zhang, M.; Wu, Y.; Qin, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 3618.
15. Dounay, A. B.; Overman, L. E.; Wrobleski, A. D. *J. Am. Chem. Soc.* **2005**, *127*, 10186.
16. (a) Grotjahn, D. B.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1990**, *112*, 5653; (b) Levy, J.; Sapi, J.; Laronze, J. Y.; Royer, D.; Toupet, L. *Synlett* **1992**, 601.
17. (a) Solé, D.; Peidró, E.; Bonjoch, J. *Org. Lett.* **2000**, *2*, 2225; (b) Solé, D.; Diaba, J.; Bonjoch, J. *J. Org. Chem.* **2003**, *68*, 5746; (c) Bonjoch, J.; Diaba, F.; Puigbó, G.; Peidró, E.; Solé, D. *Tetrahedron Lett.* **2003**, *44*, 8387; (d) Solé, D.; Urbaneja, X.; Bonjoch, J. *Adv. Synth. Catal.* **2004**, *346*, 1646; (e) Solé, D.; Urbaneja, X.; Bonjoch, J. *Org. Lett.* **2005**, *7*, 5461.
18. Padwa, A.; Brodney, M. A.; Dimitroff, M.; Liu, B.; Wu, T. *J. Org. Chem.* **2001**, *66*, 3119.
19. Hubbs, J. L.; Heathcock, C. H. *Org. Lett.* **1999**, *1*, 1315.
20. Bur, S. K.; Lynch, S. M.; Padwa, A. *Org. Lett.* **2002**, *4*, 473.
21. (a) Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 7240; (b) Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 10028.
22. (a) Sundberg, R. J.; Russell, H. F.; Ligon, W. V.; Lin, L. S. *J. Org. Chem.* **1972**, *37*, 719; (b) Murata, S.; Yoshidome, R.; Satoh, Y.; Kato, N.; Tomioka, H. *J. Org. Chem.* **1995**, *60*, 1428.
23. (a) Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 634; (b) Gololobov, Y. G.; Kasukhin, L. F. *Tetrahedron* **1992**, *48*, 1353.
24. (a) Molina, P.; Vilaplana, M. J. *Synthesis* **1994**, 1197; (b) Fresneda, P. M.; Molina, P. *Synlett* **2004**, 1; (c) Wamhoff, H.; Richardt, G.; Stölben, S. *Adv. Heterocycl. Chem.* **1995**, *64*, 159.
25. (a) Chan, J.; Faul, M. *Tetrahedron Lett.* **2006**, *47*, 3361; (b) Blanco, G.; Quintela, J. M.; Peinador, C. *Synthesis* **2008**, 1397; (c) Fresneda, P. M.; Molina, P.; Delgado, S. *Tetrahedron* **2001**, *57*, 6197; (d) Sugimori, T.; Okawa, T.; Eguchi, S.; Yashima, E.; Okamoto, Y. *Chem. Lett.* **1997**, 869; (e) Sugimori, T.; Okamoto, T.; Eguchi, S.; Kakehi, A.; Yashima, E.; Okamoto, Y. *Tetrahedron* **1998**, *54*, 7997.