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A concise formal synthesis of luotonin A

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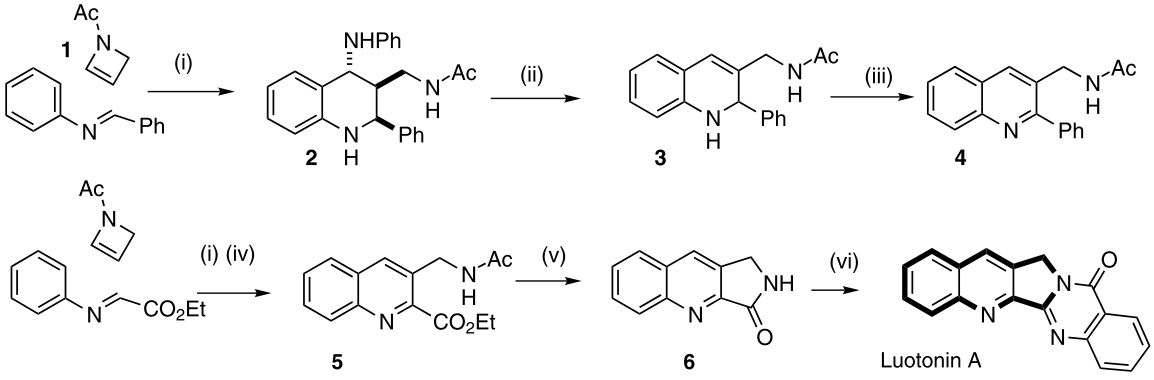
Abstract—*N*-Acetyl-2-azetine undergoes Lewis acid catalysed [4+2] cycloaddition fragmentation reactions with imines derived from aniline to give 2,3-disubstituted quinolines. This chemistry was extended to a 2-glyoxylate imine to give rapid access to an advanced precursor to the antitumour alkaloid luotonin A.

N-Acetyl-2-azetine can be easily made in multigram quantities from cheap readily available reagents and stored indefinitely at 0°C. Although this substrate has been known for a long time, its chemistry remains relatively unexplored. Heating *N*-acylazetines to high temperatures forces a [2+2]-cycloreversion to give 2-aza-dienes which can then undergo either inter- or intramolecular Diels–Alder reactions.[1,2] More recently *N*-acetyl-2-azetine has functioned as a dienophile in Diels–Alder reactions[3] and as a partner in [2+2]-photodimerisations.[4]

Recently we have been investigating the chemistry of *N*-acetyl-2-azetine **1** (Scheme 1) as a potential precursor to novel heterocycles and demonstrated that this substrate undergoes a one-pot, formal [4+2]-cycloaddition with imines derived from aromatic amines to give azetidine intermediates which react with aromatic amines under the reaction conditions to give 2,3,4-trisubstituted quinolines **2**, predominantly as the diastereoisomer shown, in high yield.[5]

We now report that this cascade can be extended further by heating the reaction mixture after formation of tetrahydroquinoline **2**. This results in a rapid elimination of aniline to give dihydroquinoline **3** which is oxidised under the reaction conditions to give 2,3-disubstituted quinoline **4** in quantitative yield. The aerial oxidation was the slow step in this sequence and by heating for shorter reaction times, 2 min reflux in acetonitrile, it proved possible to isolate the dihydroquinoline **3** in 50% yield exclusively as the tautomer depicted. This simple example demonstrates the feasibility of a one-pot, four-step process for the synthesis of 2,3-disubstituted quinolines.



Scheme 1. *Reagents and conditions*: (i) 3 mol% $Y(OTf)_3$, aniline, CH_3CN, 12 h; (ii) 2 min at 80°C; (iii) 5 h at 80°C; (iv) HCl, CH_3CN, 1 h reflux; (v) NaOEt, EtOH, 78°C; (vi) $NaN(SiMe_3)_2$, 2-sulfinylaminobenzoyl chloride.

Keywords: anti-tumour compounds; cycloadditions; enamides; quinolines.

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Luotonin A, a cytotoxic alkaloid isolated from the Chinese medicinal plant *Peganum nigellastrum*[6] is active against murine leukaemia cell line P-388 with IC_{50} 1.8 μg ml^{-1}. The 2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinoline subunit, illustrated in bold in luotonin A, is also a common structural feature in a number of other biologically interesting alkaloids, for example camptothecin, nothapodytines A and B and mappicine. Although these alkaloids have been the subject of numerous synthetic investigations,[7] new approaches are always welcome. We now report how the newly developed cyclisation fragmentation methodology can be adapted to give rapid access to luotonin A.[8]

Reaction of ethylglyoxylate aniline imine, with *N*-acetyl-2-azetine, aniline and a catalytic quantity of yttrium triflate at room temperature for 12 h gave a tetrahydroquinoline in 97% isolated yield. The attempted aromatisation of this substrate under the previously developed conditions resulted in a complex mixture of products. However, 2,3-disubstituted quinoline **5** could be isolated in 78% overall yield if a few drops of concentrated hydrochloric acid were added to the acetonitrile solution prior to the elimination aromatisation sequence. An attempt was made to retain the pendant aromatic amine in the product by oxidation with DDQ but this simply gave again quinoline **5** in 80% isolated yield, indicating that elimination of aniline was faster than the second oxidation. Finally, treatment of amide **5** with sodium ethoxide in ethanol resulted in cyclisation followed by cleavage of the resulting imide and gave lactam **6** in 99% yield. Because this lactam can be converted to luotonin A in one additional step, by reaction with 2-sulfinylaminobenzoyl chloride[8a] or isatoic anhydride,[8b] this represents a formal synthesis of this novel alkaloid. The major advantage of this approach is that structural analogues of luotonin A can be readily obtained, simply by varying the aromatic amine.

References

1. Guillemin, J. C.; Denis, J. M.; Lablachecombier, A. *J. Am. Chem. Soc.* **1981**, *103*, 468–469.
2. Jung, M. E.; Choi, Y. M. *J. Org. Chem.* **1991**, *56*, 6729–6730.
3. Dave, P. R.; Duddu, R.; Surapaneni, R.; Gilardi, R. *Tetrahedron Lett.* **1999**, *40*, 443–446.
4. Dave, P. R.; Duddu, R.; Li, J. C.; Surapaneni, R.; Gilardi, R. *Tetrahedron Lett.* **1998**, *39*, 5481–5484.
5. Osborne, D.; Stevenson, P. J. *J. Chem. Soc., Chem. Commun.* **2002**, 444–445.
6. Ma, Z. Z.; Hano, Y.; Nomura, T.; Chen, Y. J. *Heterocycles* **1997**, *46*, 541–546.
7. For recent syntheses of:
   Campothecin, see: (a) Comins, D. L.; Nolan, J. M. *Org. Lett.* **2001**, *3*, 4255–4257; (b) Yabu, K.; Masumoto, S.; Yamasaki, S.; Hamashima, Y.; Kanai, M.; Du, W.; Curran, D. P.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 9908–9909.
   Nothapodytines A and **B**, see: (c) Ishibashi, H.; Kato, I.; Takeda, Y.; Tamura, O. *Tetrahedron Lett.* **2001**, *42*, 931–933; (d) Toyota, M.; Komori, C.; Ihara, M. *J. Org. Chem.* **2000**, *65*, 7110–7113; (e) Mekouar, K.; Genisson, Y.; Leue, S.; Greene, A. E. *J. Org. Chem.* **2000**, *65*, 5212–5215.
   Mappicine, see: (f) Boger, D. L.; Hong, J. Y. *J. Am. Chem. Soc.* **1998**, *120*, 1218–1222.
8. For recent syntheses of **luotonin A**, see:
   (a) Wang, H. S.; Ganesan, A. *Tetrahedron Lett.* **1998**, *39*, 9097–9098; (b) Yadav, J. S.; Reddy, B. V. S. *Tetrahedron Lett.* **2002**, *43*, 1905–1908; (c) Dallavalle, S.; Merlina, L. *Tetrahedron Lett.* **2002**, *43*, 1835–1837; (d) Toyota, M.; Komori, C.; Ihara, M. *Heterocycles* **2002**, *56*, 101–103; (e) Kelly, T. R.; Chamberland, S.; Silva, R. A. *Tetrahedron Lett.* **1999**, *40*, 2723–2724; (f) Molina, P.; Tarraga, A.; Gonzalez-Tejero, A. *Synthesis* **2000**, 1523–1525.