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Synthesis of a novel pyrrolo-[3,2-c]quinoline N-oxide by aza-Baylis–Hillman adduct of *o*-nitrobenzaldehyde

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A B S T R A C T

A new and high yielding approach for the synthesis of a novel pyrrolo-[3,2-c]quinoline N-oxide is described. The key step consisted in the palladium-catalyzed reductive cyclization of an uncommon 3-ketopyrrole derivative of *o*-nitrobenzaldehyde, obtained in a straightforward manner through an aza-Baylis–Hillman/ring closing metathesis/aromatization reaction. A deoxygenation reaction of this novel pyrrolo-[3,2-c]quinoline N-oxide afforded a new substituted pyrrolo-[3,2-c]quinoline analogue.

Keywords:

Aza-Baylis–Hillman (aza-BH)
Ring closing metathesis (RCM)
3-Keto-pyrrole
Hexacyclic keto-nitrone
Reductive cyclization
Nitrone deoxygenation

Organic N-oxides are useful intermediates for the synthesis of biologically active compounds.^{1,2} In particular, the quinoline N-oxide core unit has been found in drugs exerting microsomal Na,K-ATPase activity,³ protein kinase inhibition and anticancer,⁴ antiviral⁵ or antimalarian activities.^{6,7} They have also relevant applications as spin traps in biological studies,⁸ and are efficient in age-related diseases,⁹ due to both in vitro and in vivo¹⁰ stability of resulting nitroxide radicals. The nitrone compound reacts with a free radical to form a derivative called spin adduct. Once the adduct is formed, it is relatively stable and the radical thus becomes inactivated and unable to interfere in biochemical processes and damage cellular tissues.

Considering the wide potential of the quinoline N-oxide core unit, and as a part of our ongoing projects on the synthesis of heterocyclic structures by ring closing metathesis (RCM),^{11–14} we decided to explore the unprecedented preparation of pyrrolo-[3,2-c]quinoline N-oxide in only one step from a biaryl system constituted by an aryl-pyrrole in which a nitro group is in δ -position with respect to the keto function. For this purpose, we extended our aza-Baylis–Hillman (aza-BH) reaction/ring closing metathesis/aromatization sequence to the preparation of an original 2-aryl-3-keto-substituted pyrrole. Aza-BH is a powerful reaction extensively exploited for the synthesis of multifunctional synthons in organic synthesis.¹⁵ It allows the formation of carbon–carbon bonds under mild reaction conditions and it consists

in the reaction between protected ammonia [usually with a sulfonyl group such as tosyl (Ts)]^{11,16,17}, an aldehyde, and a α,β -unsaturated carbonyl compound, catalyzed by nucleophilic Lewis bases such as 1,4-diazabicyclo[2,2,2]octane (DABCO).

The synthesis of 4-ethyl-1-methyl-1*H*-pyrrolo-[3,2-c]quinoline N-oxide **9** is described in Scheme 1.

In the first step, the unsaturated β -aminoketone **4a** was synthesized in a combined Lewis acid-[Ti(O*i*Pr)₄] and base-catalyzed (DABCO) three component reaction involving commercial *p*-toluenesulfonamide **2** in the presence of an excess of *o*-nitrobenzaldehyde **1**, and penten-2-one **3** as Michael acceptor.¹⁷ The reaction was performed at room temperature, with a moderate selectivity between the formation of β -aminoketone **4a** (51% yield) and β -hydroxyketone **4b** (38% yield). A worse selectivity was obtained in the absence of Lewis acid. Extensive degradation of the crude was observed by running the reaction at a temperature of 100 °C using microwave irradiation (MW) for only 10 min. This maybe due to the instability of the Michael acceptor under these conditions. We also performed the reaction under different conditions (DABCO in *i*-PrOH) to drive the reaction to completion, but concomitant formation of the corresponding hydroxyester **4b** was not avoided. All the attempts to separate **4a** from **4b** by crystallization at different temperatures and using different solvent combinations were unsuccessful, leading always to the degradation of the crude. β -Aminoketone **4a** was eventually recovered after purification by column chromatography and allylated with allyl bromide in a 'spot to spot' reaction in the presence of K₂CO₃ in DMF¹⁴ to yield 83% of the corresponding diene **5**. The reaction was

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Scheme 1. Synthesis of 4-ethyl-1-methyl-1H-pyrrolo-[3,2-c]quinoline N-oxide **9**.

performed either at room temperature within 12 h or under microwave irradiation at 100 °C for only 10 min without affecting the yield. After purification by chromatography, diene **5** was subsequently submitted to the ring closing metathesis (RCM) reaction known to be an efficient method for the synthesis of heterocyclic structures from linear precursors.^{18–21} Cyclization of diene **5** bringing to the novel conjugated cyclic enone **6** was complete within 12 h at room temperature using 5% 2nd generation air stable Grubbs' catalyst in good yield. Attempts to accelerate the reaction by microwave (100 °C, CH₂Cl₂)¹⁶ were unsuccessful, due to degradation of the starting material.

Few examples for the formation of 3-carboxy-substituted five membered heterocyclic alkenes through RCM reaction^{22–26} are reported, as well as their synthesis starting from aza-BH adducts,^{11,16,17,27,28} but none of them focus on the synthesis of 2-aryl-3-keto-substituted pyrrole according to this procedure.

The next step was cleavage of the tosyl group.^{29–31} Using *t*-BuOK in DMF at room temperature, 47% of the substituted pyrrole **7** was obtained within 2.5 h via elimination/aromatization steps. We supposed that the moderate yield resulted from the isomerization of pyrroline, or to secondary reactions involving the enol form of ketone. Then, pyrrole **7** was reacted with methyl iodide³² in the presence of Cs₂CO₃ in DMF to yield the corresponding methylated pyrrole **8** in high yield. Similar structures, in which a methyl group is used to protect pyrrole ring, have been synthesized to afford very potent antiviral, antibacterial and anticancer agents.^{33,34} Directly used without any purification, methyl-protected pyrrole **8** was hydrogenated at room temperature in methanol using Pd/C under H₂ atmosphere,³⁵ yielding a very polar compound, which was identified as the stable hitherto unknown 4-ethyl-1-methyl-1H-pyrrolo-[3,2-c]quinoline N-oxide **9**³⁶ with the nitrone function confined to a ring structure in good yield, after purification by column chromatography. The conversion was not quantitative and 16% of the starting material was still present in the mixture, as determined by ¹H NMR of the crude. The synthesis of differently substituted quinoline N-oxides has been described starting from the Baylis-Hillman adduct of *o*-nitrobenzaldehyde: in acidic medium, to access penta-³⁷ or hexa-cyclic^{38,39} nitrone, or through an hydrogenation/cyclization cascade reaction,⁴⁰ but no examples are reported for pyrrolo-quinoline N-oxide structures.

When the hydrogenation reaction was prolonged for more than 12 h, N–O hydrogenolysis/deoxygenation process occurred and a side reaction involving pyrrolo-quinoline N-oxide **9** yielded imine

10 (Scheme 1). The last compound was recovered by column chromatography in a moderate yield, along with traces of the corresponding amine.

In conclusion, an efficient synthesis of 2-substituted-3-keto-pyrrole has been developed, through a sequential aza-BH/ring closing metathesis/aromatization as a novel route to access to a novel hexacyclic nitrone, after palladium-catalyzed reductive cyclization. A deoxygenation reaction provides also an easy conversion into the imine. Biological tests are in progress to evaluate the full potential of the novel structure presented here.

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References and notes

- Merino, P. *Science of Synthesis*; Padwa, A., Ed.; Thieme: Stuttgart, 2004; Vol. 27, pp 511–580.
- Pyne, S. G.; Minyan, T. *Curr. Org. Chem.* **2005**, *9*, 1393–1418.
- Andreev, V. P.; Korvacheva, E. G.; Nizhnik, Y. P. *Pharm. Chem. J.* **2006**, *40*, 347–348.
- Capraro, H.-G.; Furet, P.; Garcia-Echeverria, C.; Stauffer, F.; WO 2005054238, 2005, p 138.
- Albrecht, T.; Spleelman, D. J.; Sadagopa Ramanujam, V. M.; Lund, H. W.; Legator, M. S.; Trieff, N. M. *Terat. Carcin. Mut.* **1980**, *1*, 161–169.
- Werbel, L. M.; Kersten, S. J.; Turner, W. R. *Eur. J. Med. Chem.* **1993**, *28*, 837–852.
- Mouaddib, A.; Joseph, J.; Hasnaoui, A.; Mèrou, Y.-J. *Synthesis* **2000**, *4*, 549–556.
- Zhang, H.; Joseph, J.; Vasquez-Vivar, J.; Karoui, H.; Nsanzumuhire, C.; Martasek, P.; Tordo, P.; Kalyanaraman, B. *FEBS Lett.* **2000**, *473*, 58–62.
- Floyd, R. A. *Aging Cell* **2006**, *5*, 51–57.
- Green, A. R.; Ashwood, T.; Odergren, T.; Jackson, D. M. *Pharmacol. Ther.* **2003**, *100*, 195–214.
- (a) Declercq, V.; Allouchi, H.; Martinez, J.; Lamaty, F. *J. Org. Chem.* **2007**, *72*, 1518–1521; (b) Benakki, H.; Colacino, E.; André, C.; Guenoun, F.; Martinez, J.; Lamaty, F. *Tetrahedron* **2008**, *64*, 5949–5955.
- Varray, S.; Gauzy, C.; Lamaty, F.; Lazaro, R.; Martinez, J. *J. Org. Chem.* **2000**, *65*, 6787–6790.
- Varray, S.; Lazaro, R.; Martinez, J.; Lamaty, F. *Eur. J. Org. Chem.* **2002**, 2308–2316.
- Varray, S.; Lazaro, R.; Martinez, J.; Lamaty, F. *Organometallics* **2003**, *22*, 2426–2435.
- Shi, Y.-L.; Shi, M. *Eur. J. Org. Chem.* **2007**, 2905–2916.
- Declercq, V.; Ribière, P.; Martinez, J.; Lamaty, F. *J. Org. Chem.* **2004**, *69*, 8372–8381.
- Balan, D.; Adolfsson, H. *Tetrahedron Lett.* **2004**, *45*, 3089–3092.
- Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199–2238.
- Felpin, F.-X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 3693–3712.

20. Phillips, A. J.; Abell, A. D. *Aldrichim. Acta* **1999**, 32, 75–90.
21. Donohoe, T. J.; Orr, A. J.; Bingham, M. *Angew. Chem., Int. Ed.* **2006**, 45, 2664–2670.
22. Rhee, J. U.; Krische, M. J. *Org. Lett.* **2005**, 7, 2493–2495.
23. Grigg, R.; Martin, W.; Morris, J.; Sridharan, V. *Tetrahedron* **2005**, 61, 11380–11392.
24. Grigg, R.; Hodgson, A.; Morris, J.; Sridharan, V. *Tetrahedron Lett.* **2003**, 44, 1023–1026.
25. Grigg, R.; Martin, W.; Morris, J.; Sridharan, V. *Tetrahedron Lett.* **2003**, 44, 4899–4901.
26. Yang, S.-H.; Caprio, V. *Synlett* **2007**, 1219–1222.
27. Kim, J. M.; Lee, K. Y.; Lee, S.; Kim, J. N. *Tetrahedron Lett.* **2004**, 45, 2805–2808.
28. Yang, C.; Murray, W. V.; Wilson, L. J. *Tetrahedron Lett.* **2003**, 44, 1783–1786.
29. Declerck, V.; Allouchi, H.; Martinez, J.; Lamaty, F. J. *Org. Chem.* **2007**, 72, 3158.
30. Kundu, N. G.; Nandi, B. J. *Org. Chem.* **2001**, 66, 4563–4575.
31. Nandi, B.; Kundu, N. G. *Org. Lett.* **2000**, 2, 235–238.
32. Tao, Y. T.; Chen, M. L. J. *Org. Chem.* **1988**, 53, 69–72.
33. Gerster, J. F.; Lindstrom, K. J.; Miller, R. L.; Tomai, M. A.; Birmachu, W.; Bomersine, S. N.; Gibson, S. J.; Imbertson, L. M.; Jacobson, J. R.; Knafla, R. T.; Maye, P. V.; Nikolaidis, N.; Oneyemi, F. Y.; Parkhurst, G. J.; Pecore, S. E.; Reiter, M. J.; Scribner, L. S.; Testerman, T. L.; Thompson, N. J.; Wagner, T. L.; Weeks, C. E.; Andre, J.-D.; Lagain, D.; Bastard, Y.; Lupu, M. J. *Med. Chem.* **2005**, 48, 3481–3491.
34. Kuyper, L. F.; Baccanari, D. P.; Jones, M. L.; Hunter, R. N.; Tansik, R. L.; Joyner, S. S.; Boytos, C. M.; Rudolph, S. K.; Knick, V.; Wilson, H. R.; Caddell, J. M.; Friedman, H. S.; Comley, J. C. W.; Stables, J. N. J. *Med. Chem.* **1996**, 39, 892–903.
35. Zschiesche, R.; Reissig, H.-U. *Tetrahedron Lett.* **1988**, 29, 1685–1686.
36. *Experimental procedure for the synthesis of 4-ethyl-1-methyl-1H-pyrrolo-[3,2-c]quinoline N-oxide (9)*: To a solution of **8** (252 mg, 0.98 mmol) in methanol (100 mL) was added palladium on charcoal (10%, w/w). The mixture was placed under hydrogen atmosphere. After 12 h at room temperature, the mixture was filtered over Celite and the Celite pad was washed with methanol. The solvent was evaporated and after column chromatography over silica gel and AcOEt/Et₂O (1/9 to 2/8) as developing solvent yields 181 mg (82%) of **9** as a white powder. Mp 168–172 °C; ¹H NMR [(CD₃)₂CO, Me₄Si] δ (ppm): 8.85 (m, 1H), 8.41 (m, 1H), 7.58 (m, 2H), 7.31 (d, J = 3.1 Hz, 1H), 6.61 (d, J = 3.1 Hz, 1H), 4.21 (s, 3H), 3.21 (q, J = 7.4 Hz, 2H), 1.25 (t, J = 7.4 Hz, 3H); ¹³C NMR [(CD₃)₂CO, Me₄Si] δ (ppm): 145.2, 138.2, 131.8, 127.2, 126.8, 126.5, 125.9, 121.6, 121.5, 120.9, 119.2, 37.6, 22.1, 10.29; IR (KBr): 3415.7 (br), 2978.5 (w), 2216.8 (w), 1633.0 (m), 1508.2 (s), 1446.9 (m), 1217.8 (s), 1118.7 (m), 1101.0 (s), 1026.1 (m), 903.4 (s), 764.9 (s) cm⁻¹; ESI-MS m/z 453.2 [2M+H]⁺; 227.0 [M+H]⁺; FAB(+) m/z 227.1 [M+H]⁺; HRMS calcd for C₁₄H₁₅ON₂ 227.1184; found: 227.1202.
37. Lee, M. J.; Lee, K. Y.; Park, D. Y.; Kim, J. N. *Bull. Korean Chem. Soc.* **2005**, 26, 1281–1285.
38. Kim, J. N.; Lee, K. Y.; Kim, H. S.; Kim, T. Y. *Org. Lett.* **2000**, 2, 343–345.
39. Lee, K. Y.; Kim, J. M.; Kim, J. N. *Tetrahedron* **2003**, 59, 385–390.
40. Familioni, O. B.; Kaye, P. T.; Klaas, P. J. *Chem. Commun.* **1998**, 2563–2564.