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A rare pyridine to pyrrole conversion leading to a side product in epoxide ring opening

Charles Pathirana [a,*], Rajesh Shukla [a], John Castoro [a], Douglas Weaver [b], Liam Byrne [c], Gaelle Pennarun-Thomas [c], Venkatapuram Palaniswamy [a]

[a] Analytical R&D, R&D, Bristol-Myers Squibb, New Brunswick, NJ 08903, USA
[b] Technical Operations, Bristol-Myers Squibb, Syracuse, NY 13057, USA
[c] Technical Operations, Bristol-Myers Squibb, Swords, Ireland

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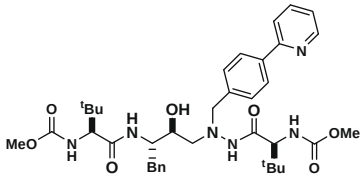
ABSTRACT

A minor side product in a manufacturing batch of the intermediate **4** was observed and separated. The minor side product **5** was purified by preparative HPLC and its structure was determined by the analysis of comprehensive NMR and MS data. The structure of **5** reveals that its mechanism of formation includes a rare conversion of a pyridine moiety to a pyrrole.

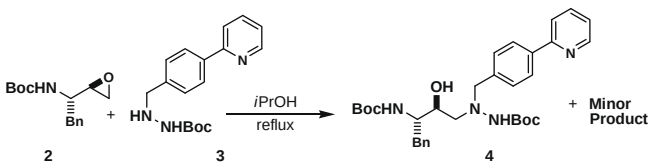
Active pharmaceutical ingredients (APIs) are manufactured using syntheses derived from early laboratory experimentation. In order to obtain the desired results during the scale-up operations, careful attention has to be paid to the details of the synthesis. Optimization of the synthesis for large scale through process development ensures a robust process that is practical and delivers products of desired quality; however, slight, inevitable variations in chemistry due to the scale effects in some cases may lead to undesired side products. When undesired side products are observed, it is essential that they are identified to understand the anomalous behavior and further optimize the process. The undesired products are often isolated in a pure form, and the structural elucidation is carried out using spectroscopic techniques.



1

Atazanavir (**1**) is a potent HIV-protease inhibitor containing an aza-dipeptide moiety.[1,2] The first intermediate **4** that contains this structural fragment is prepared as shown in Scheme 1. **2** and **3** in refluxing isopropanol give **4** as the main product. A minor side product was consistently observed when the process was scaled up in manufacturing. The structure of the minor side product **5** was elucidated by NMR and mass spectrometry (MS).[3] As shown, the minor side product **5** contains a pyrrole suggesting a rare pyridine to pyrrole rearrangement, which appears to have resulted from the reaction of **4** with excess of the epoxide **2**.

The minor side product **5** from the coupling reaction described in Scheme 1 was isolated and purified by preparative HPLC as a white solid. Its molecular formula of $C_{47}H_{63}N_5O_9$ was established using the exact mass of $[M+H]^+$ determined by positive ESI HRMS (observed 842.4694, calculated 842.4704). Comparison of the elemental compositions of **4** and the side



2 3 4

Scheme 1.

* Corresponding author. Tel.: +1 732 227 7418; fax: +1 732 227 3934.
E-mail address: charles.pathirana@bms.com (C. Pathirana).

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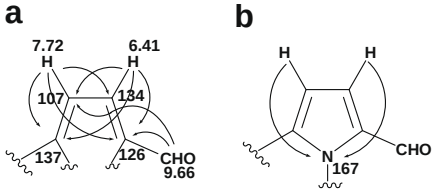
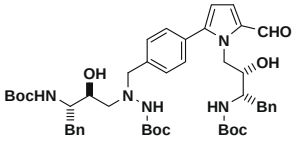


Figure 1. Heteronuclear multiple bond correlations (HMBC), (a) $^{1}H–^{13}C$ correlations, (b) $^{1}H–^{15}N$ correlations. The numbers beside the atoms denote chemical shifts δ in ppm relative to DMSO-d_6 at δ 2.49 for ^{1}H, δ 39.5 for ^{13}C and NH_3 (external) at δ 0.0 for ^{15}N.

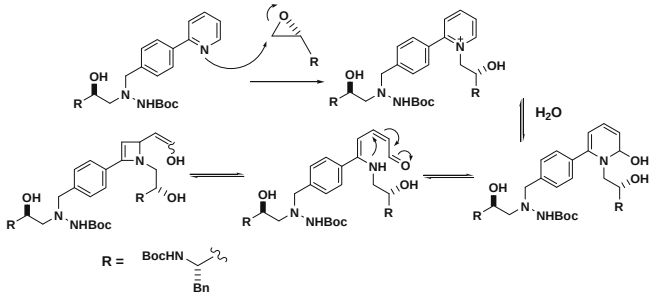
product **5** indicates that **5** arises from an extended reaction where addition of two molecules of epoxide to one molecule of the hydrazine has taken place. The product ions generated from the protonated molecule $[M+H]^+$ of the 841 Da side product provided useful information.[4] The fragment ion at *m/z* 542 ($[M+H]^+ -3$ Boc) indicated that **5** contained 3 Boc groups. **4** produced a fragment ion at *m/z* 168 corresponding to a 1-methyl-4-pyridylphenyl fragment. The absence of this ion in the fragmentation of **5** indicates that **5** contains, if present, a modified 2-phenylpyridine moiety. Supporting this observation, ^{1}H NMR spectrum of **5** lacked the characteristic four multiplets assigned to the four protons on the pyridine ring of **4**. Instead, there were three singlets at δ 6.41, 7.72, and 9.66, of which the last indicated the presence of an aldehyde.

Long-range correlations observed in a $^{1}H–^{13}C$ HMBC experiment clearly showed that these protons and 5-carbons form an isolated fragment in the molecule. This 5-carbon structural fragment is shown in Figure 1a. The two protons in the above structural fragment showed correlations to a nitrogen at δ 167 in a $^{1}H–^{15}N$ HMBC experiment. These correlations supported the insertion of a nitrogen into the above structural fragment to form a pyrrole ring as shown in Figure 1b. All the NMR data are in agreement with the structure **5** assigned to the minor side product.[5]



5

The formation of **5** indicates a rare conversion of a pyridine to a pyrrole.[6,7] This conversion proceeds via opening of a second epoxide ring by the attack of pyridine nitrogen resulting in the first intermediate, a pyridinium salt (Scheme 2). This may then undergo opening of the pyridine ring to yield an aldehyde. Ring opening of pyridinium salts is described in the well-known Zincke reaction and the resulting aldehyde is known as Zincke aldehyde.[8–10] The hydroxy group (β to N^+) on the side chain of the salt may facilitate this transformation by the formation of an aminal that may be hydrolyzed to yield the aldehyde. It is likely that this intermediate aldehyde proceeds through a 1,2-dihydroazete which may rearrange under thermal conditions to produce a pyrrole.[11] The side



Scheme 2.

product (**5**) was observed at a level as high as 1.6%. Compound **5** was undetectable when the coupling reaction was carried out under inert conditions.

Conclusion

A minor side product isolated from a coupling reaction between an epoxide and a hydrazine containing a pyridine ring was identified as a pyrrole that arises from an addition of a second molecule of the epoxide to the pyridine moiety in the starting material. The complete identification of the pyrrole containing side product was achieved using NMR and MS. The structure of the side product indicates a rearrangement of the pyridine moiety to produce a pyrrole.

Acknowledgments

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References and notes

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2. Fassler, A.; Bold, G.; Steiner, H. *Tetrahedron Lett.* **1998**, *39*, 4925.
3. This work was first presented at SMASH, Small Molecule NMR Conference, Verona, Italy, September, 2005.
4. HRMS/MS (+ve ESI): *m/z* 842.4694 ($[M+H]^+$, −1.2 ppm, $C_{47}H_{64}N_5O_9$); 786.4105 (+3.4 ppm, $C_{43}H_{56}N_5O_9$); 742.4180 (0.0 ppm, $C_{42}H_{56}N_5O_7$); 686.3575 (+3.1 ppm, $C_{38}H_{48}N_5O_7$); 642.3685 (+4.6 ppm, $C_{37}H_{48}N_5O_5$); 586.3068 (+6.6 ppm, $C_{33}H_{40}N_5O_5$); 542.3160 (+5.3 ppm, $C_{32}H_{40}N_5O_3$).
5. ^{1}H NMR (600.13 MHz, DMSO-d_6): δ 9.66 (s, 1H), 7.72 (br s, 1H), 7.1–7.4 (m, 14H), 6.41 (br s, 1H), 4.01 (br d, J = 13 Hz, 1H), 3.90 (br s, 2H), 3.83 (br dd, J = 9.6, 13.0 Hz, 1H), 3.75 (m, 1H), 3.69 (br s, 1H), 3.61 (m, 1H), 3.54 (m, 1H), 2.77 (m, 1H), 2.81 (m, 1H), 2.67 (m, 3H), 2.60 (m, 1H), 1.26 (br s, 27H); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 185.6, 156.2, 155.7, 139.5, 139.2, 137.0, 133.3, 130.2, 129.4, 129.3, 129.1, 128.8, 128.4, 126.3, 126.2, 125.3, 106.6, 78.2, 78.0, 71.1, 68.4, 61.4, 60.6, 54.7, 53.8, 50.7, 37.3, 36.5, 28.4.
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