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Tetrahedron Letters 47 (2006) 4553–4556
Tetrahedron Letters

Selective functionalizations of 2-phenylpyridine: lactones upon organic versus organometallic activations

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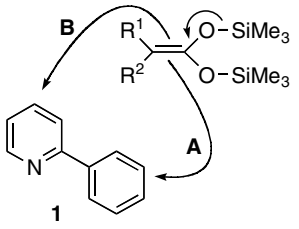
Received 23 March 2006; revised 26 April 2006; accepted 2 May 2006
Available online 22 May 2006

Abstract—2-Phenylpyridine activated by chromium tricarbonyl reacts with bis(TMS) ketene acetals to give pyridine-substituted bicyclic γ-lactones. On the other hand, its reaction with the same acetals leads, upon activation with methylchloroformate, to dihydropyridines which can be oxidized to highly substituted, lactone-containing piperidines.

The lactone function is the pharmacophore of many natural and nonnatural molecules possessing important biological properties: lactones fused to heterocycles are part of this class of compounds.[1–5] During our ongoing research in this area, we were faced with the problem of the selective functionalization of 2-phenylpyridine **1** and more precisely with the introduction of a lactone function on each of the two aromatic rings. Although, both substituted benzene and pyridine rings had already been submitted separately to such modifications,[6–13] the easy introduction of such functions in this substrate was not obvious for steric and electronic reasons.

The goal of this communication is to show that this can nevertheless be achieved by first activating the phenyl ring with a metal, in this case chromiumtricarbonyl (route A), and second, by activating the pyridine ring with an acylium ion (route B), both intermediate 'complexes' undergoing a double nucleophilic addition of a 1,3-C,O-dinucleophile originating from a bis(TMS) ketene acetal[14–16] (Scheme 1). As far as the first attempt is considered, in contrast to the two other isomers of phenylpyridine which gave only the nitrogen coordinated chromiumpentacarbonyl complexes,[17] 2-phenylpyridine **1** reacts with chromium hexacarbonyl, according to the literature,[18] to give the expected chromium tricarbonyl complex **2** in 63% yield as a yellow solid mp 120 °C.



Scheme 1.

The addition of the ketene acetal **3a** to complex **2** in THF/DMF, in the presence of a twofold excess of a molar solution of *t*-BuOK in THF, at −76 °C and stirring for 4 h, was followed by the addition of an excess of iodine in THF (4 equiv) at the same temperature. The solution was kept at room temperature overnight and iodine in excess eliminated. Work up led to a mixture of two compounds which were separated by silica gel chromatography (Scheme 2). As a consequence of the NMR data,[19] structure **4a** was given to the less polar product, isolated in 18% yield as white crystals mp 162 °C, an acid resulting from the *ortho* addition of the ketene acetal acting as a C-nucleophile to the phenyl ring of phenylpyridine, followed by a iodine-induced rearomatization.[20,21]

According to its physical properties,[22] the more polar product **5a** (13%) is not an acid but a lactone (δCO,

Keywords: Phenylpyridine; Bis(TMS) ketene acetals; Nucleophilic additions; γ- and δ-Lactones.
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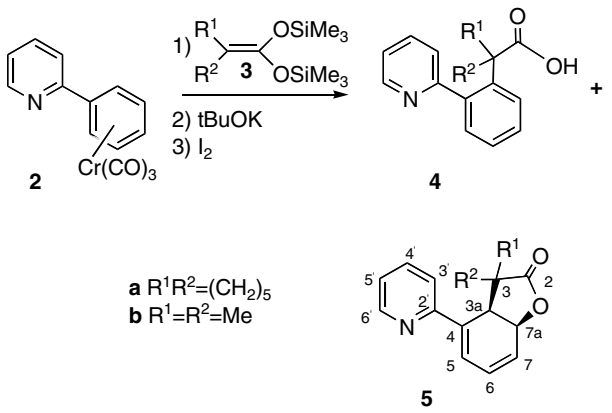
doi:10.1016/j.tetlet.2006.05.006



Scheme 2.

182.2 ppm) showing in the ^{1}H NMR spectrum besides the signals for the protons of the pyridine ring, signals for three adjacent vinylic protons, and a highly deshielded signal at δ 5.61 ppm typical for the protons on the carbon bearing the oxygen function of the lactones.[8] $^{1}H,^{1}H$ and $^{1}H,^{13}C$ correlation spectra clearly indicated that this compound had structure **5a**. An X-ray analysis (Fig. 1) confirmed the *ortho*, *meta* addition of the dinucleophile, leading to a γ-lactone, the ring junction being cis.

This is the first example of the double nucleophilic addition of such a ketene acetal to a substituted phenyl ring in which the addition of the C-nucleophile takes place at the *ortho* position. Indeed, both in aromatic rings bearing electron-attracting or electron-releasing substituents, this addition occurred either at the meta or at the para positions.[8] This special selectivity can be inferred to an *ortho* directing effect of the nitrogen atom of the pyridine nucleus. Complex **2** reacted similarly with ketene acetal **3b** to give a mixture of acid **4b** (6%) and lactone **5b** (7%). When instead the enolate was prepared from the TMS ester ($R^{1}R^{2}$=$(CH_2)_5$) and LDA, although a mixture of the corresponding acids and lactones was observed, the yield of the acid, 49%, was much better, the yield of the lactone (11%) being roughly the same. In spite of the fact that the yields of lactones are much lower than for other substituted aromatic ring systems, this approach allows for the desired functionalization of the phenyl ring in 2-phenylpyridine. Lets now consider the transformation of the pyridine moiety.

In a previous paper,[12] we already described the sluggish reactivity of 2-phenylpyridine activated by methylchloroformate towards ketene acetals **3**. Under the usual conditions (1.5 equiv of acetal, 3 equiv of methylchloroformate, 2 h at room temperature), this substrate led to a low 15% yield of the expected 1,4-dihydropyridine **6** (Scheme 3). The yield could however be substantially increased by leaving the reaction for 12 h (70% yield according to the NMR, 35% isolated product). When dihydropyridine **6** was reacted with a twofold excess of *m*-chloroperbenzoic acid in diethylether at room temperature,[13] for two days, a slow reaction took place leading to a polar, poorly soluble crystalline compound, mp 206 °C, in 35% yield[23] (Scheme 4). According to its NMR data,[24] this compound neither is an acid, nor contains a carbon–carbon double bond, thus is not the expected hydroxylactone **7** (Scheme 5).

The mass spectrum confirmed that an extra oxygen had been introduced in the hypothetical **7**.

Crystals suitable for an X-ray analysis (Fig. 2) could be grown from dichloromethane solutions.[25] Fig. 2 shows that indeed the expected δ-lactone is present as it should be in **7**, but that an intramolecular interaction of the hydroxyl group of **7** with the carbon–carbon double bond took place, giving a new lactone fused to a hydroxytetrahydrofurane. Surprisingly, the oxygen bridge and the hydroxyl group are cis, a geometry which is not in agreement with an intramolecular ring-opening of a presumed intermediate epoxide. The transformation of **7**

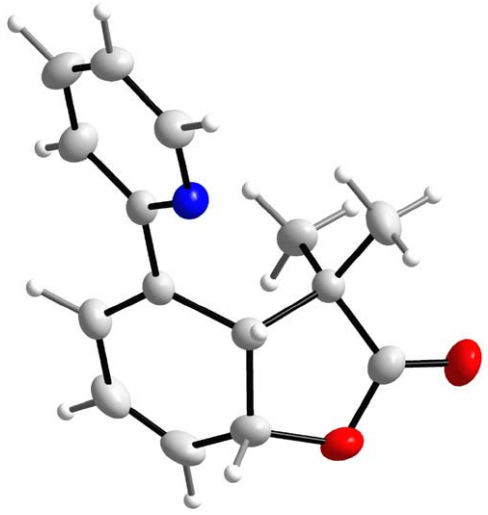
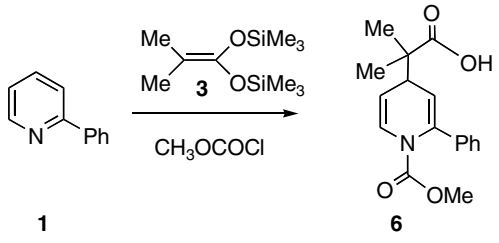
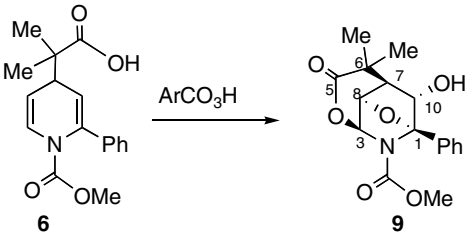


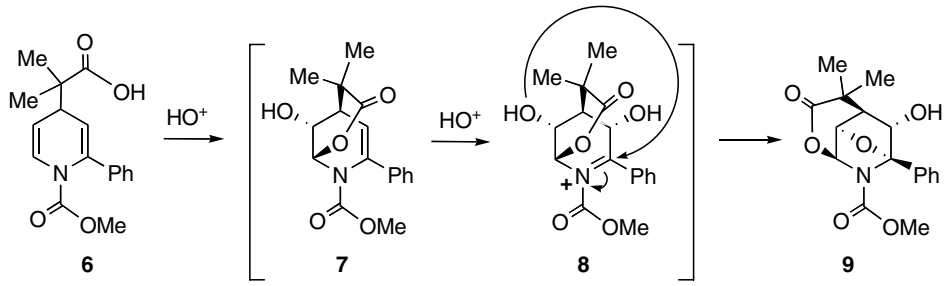
Figure 1. Diamond view of lactone **5b**.



Scheme 3.



Scheme 4.



Scheme 5.

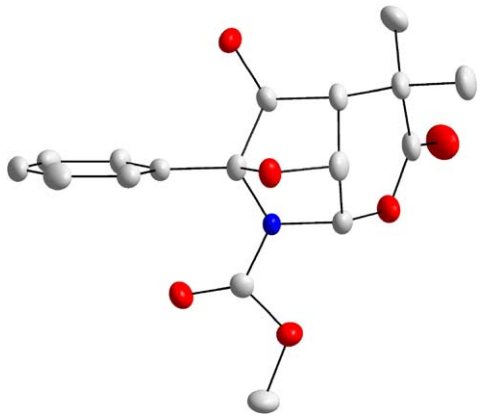


Figure 2. Diamond view of lactone **9**.

into **9** would rather involve the formation of an epoxide trans to the lactone ring which opens-up to give an iminium **8**. An intramolecular addition of the hydroxyl group to C-1 might then give **9** (Scheme 5).

Thus, up to five stereogenic centers can be formed in two steps from 2-phenylpyridine **1** in a high stereoselective way leading to a polysubstituted piperidine.[26–31]

A further goal of these transformations will thus be the preparation in an enantioselective way of these types of polycyclic lactones.

Acknowledgments

ECOS-NORD, ANUIES/CONACYT (Contract M02P04 France-Mexico) are acknowledged for financial support.

References and notes

1. Hoffmann, H. M. R.; Rabe, J. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 94–110.
2. Koch, S. S. C.; Chamberlain, A. R. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier Science B.V.: Amsterdam, The Netherlands, 1995; Vol. 16, pp 687–725.
3. Han, G.; LaPorte, M. G.; Folmer, J. J.; Werner, K. M.; Weinreb, S. M. *J. Org. Chem.* **2000**, *65*, 6293–6306.
4. Alibes, R.; Ballbe, M.; Busque, F.; de March, P.; Elias, L.; Figueredo, M.; Font, J. *Org. Lett.* **2004**, *6*, 1813–1816.
5. Sibi, M. P.; Subramanian, T. *Synlett* **2004**, *7*, 1211–1214.
6. Bellassoued, M.; Chelain, E.; Collot, J.; Rudler, H.; Vaissermann, J. *Chem. Commun.* **1999**, 187–188.
7. Rudler, H.; Parlier, A.; Cantagrel, F.; Bellassoued, M. *Chem. Commun.* **2000**, 771–772.
8. Rudler, H.; Comte, V.; Garrier, E.; Bellassoued, M.; Chelain, E.; Vaissermann, J. *J. Organomet. Chem.* **2001**, *621*, 284–298.
9. Rudler, H.; Harris, P.; Parlier, A.; Cantagrel, F.; Denise, B.; Bellasssoued, M.; Vaissermann, J. *J. Organomet. Chem.* **2001**, *624*, 186–202.
10. Rudler, H.; Alvarez, C.; Parlier, A.; Aldeco-Perez, E.; Denise, B.; Xu, Y.; Vaissermann, J. *Tetrahedron Lett.* **2004**, *45*, 2409–2411.
11. Rudler, H.; Denise, B.; Parlier, A.; Daran, J. C. *Chem. Commun.* **2002**, 940–941.
12. Rudler, H.; Denise, B.; Xu, Y.; Parlier, A.; Vaissermann, J. *Eur. J. Org. Chem.* **2005**, 3724–3749.
13. Rudler, H.; Denise, B.; Xu, Y.; Vaissermann, J. *Tetrahedron Lett.* **2005**, *46*, 3449–3451.
14. For the synthesis of bis(TMS) ketene acetals see: Ainsworth, C.; Kuo, Y.-N. *J. Organomet. Chem.* **1972**, *46*, 73–87.
15. For recent applications of this methodology see: Ullah, E.; Rotzoll, S.; Schmidt, A.; Michalik, D.; Langer, P. *Tetrahedron Lett.* **2005**, 8997–8999.
16. Ullah, E.; Langer, P. *Synlett* **2004**, *15*, 2782–2784.
17. Unpublished results.
18. Djukic, J. P.; Maisse, A.; Pfeffer, M. *J. Organomet. Chem.* **1998**, *567*, 65–74.
19. ^{1}H NMR of **4b** (200 MHz, $CDCl_3$): δ 1.54 (s, 6H, $(CH_3)_2CH$); 7.16 (dd, 1H, $J = 4$ Hz); 7.38 (m, 2H); 7.51 (m, 1H); 7.62 (m, 3H); 8.60 (d, 1H), 11.00 (s, 1H, CO_2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 180.18 (CO); 157.21, 148.8, 146.42, 138.0, 136.67, 127.46, 126.39, 122.47, 121.90, 46.50, 26.62.
20. For the addition of nucleophiles to arenetricarbonylchromium complexes see for example: McQuillin, F. J.; Parker, D. G.; Stephenson, G. R. In *Transition Metal Organometallics for Organic Synthesis*; Cambridge University Press: Cambridge, UK, 1991; pp 182–231.
21. For transition metal mediated dearomatization reactions see: Pape, A. R.; Kaliappan, K. P.; Kündig, E. P. *Chem. Rev.* **2000**, *100*, 2917–2940.
22. Lactones **5b** ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53 (d, 1H, $J = 8$ Hz, $H^{6'}$), 7.63 (m, 1H, $H^{4'}$), 7.42 (d, 1H, $J = 8$ Hz, $H^{3'}$), 7.13 (dd, 1H, $J = 2$ and 8 Hz, $H^{5'}$), 6.46 (d, 1H, $J = 10$ Hz, H^{5}), 6.00 (m, 1H, H^{6}), 5.78 (dd, $J = 2$ and 10 Hz, H^{7}), 5.61 (m, 1H, H^{7a}), 4.23 (d, 1H, $J = 12$ Hz, H^{3a}), 1.01 and 1.07 (s, 6H, 2 CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.2, 26.4 (CH_3), 42.0 (C^{3}), 42.5 (C^{3a}), 76.9 (C^{7a}), 120.6 ($C^{3'}$), 122.7 ($C^{5'}$), 123.15 (C^{5}), 125.1 (C^{7}), 136.3 (C^{4}), 136.7 ($C^{4'}$), 149.13 ($C^{6'}$), 156.5 ($C^{2'}$), 182.2 (CO). Compound **5a** ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.50 (d, 1H, $J = 8$ Hz, $H^{6'}$), 7.65 (m, 1H, $H^{4'}$), 7.43 (m, 1H, $H^{3'}$), 7.20 (m, 1H, $H^{5'}$), 6.40 (d, 1H, $J = 6$ Hz, H^{5}), 5.98

(m, 1H, H^6), 5.80 (dd, 1H, $J = 2$ and 10 Hz, H^7), 5.56 (m, 1H, H^{7a}), 4.10 (d, 1H, $J = 12$ Hz, H^{3a}), 1.07–1.67 (m, 10H, $(CH_2)_5$). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 179.96 (CO), 157.17 ($C^{2'}$), 149.20 ($C^{6'}$), 136.86 ($C^{4'}$), 136.08 (C^4), 126.42 (C^7), 125.01 (C^6), 124.49 (C^5), 122.74 ($C^{5'}$), 120.99 ($C^{3'}$), 77.16 (C^{7a}), 43.77 ($C^{3,3a}$), 21.10–29.24 ($(CH_2)_5$).

23. For a general review on non-biomimetic reactions of dihydropyridines and applications see: Lavilla, R. *J. Chem. Soc., Perkin Trans.1* **2002**, 1141–1156; See also: Lavilla, R.; Baron, X.; Coll, O.; Gullon, F.; Masdeu, C.; Bosch, J. *J. Org. Chem.* **1998**, *63*, 10001–10005; Zhao, G.; Deo, U. C.; Ganem, B. *Org. Lett.* **2001**, *3*, 201–203.
24. Lactone **9** ^1H NMR (200 MHz, $CDCl_3$): δ 7.37–7.54 (m, 5H, C_6H_5), 5.95 (d, 1H, $J = 4$ Hz, H^3), 4.94 (dd, 1H, $J = 4$ and 5 Hz, H^8), 4.43 (m, 1H, H^{10}), 3.42 (s, 3H, OCH_3), 3.32 (m, 1H, H^7), 1.43 and 1.45 (s, 6H, $(CH_3)_2C$); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 173.71 (CO), 151.76 (CO_2Me), 128.23–129.78 (C_6H_5), 100.49 (C^1), 87.06 (C^3), 76.46 (C^{10}), 70.27 (C^8), 58.45 (C^7), 52.87 (OCH_3), 39.64 (C^6), 24.14 and 29.61 ($(CH_3)_2C$).
25. Crystal data for **5b** and **9**, CCDC 232997 and 298171, can be obtained free of charge from the Cambridge Data Centre via www.ccdc.ac.uk/data.report/cif.
26. For the synthesis of piperidines see for example: Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781–1813.
27. For the biological properties of piperidines see: Beak, P.; Stehle, N. W.; Wilkinson, T. J. *Org. Lett.* **2000**, *2*, 155–158.
28. O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435–446.
29. Elliot, R. L.; Kopecka, H.; Lin, N.-H. Y.; He, H.; Garvey, D. S. *Synthesis* **1995**, 772–774.
30. Basha, F. Z.; Debernadis, J. F. *Pure Appl. Chem.* **1994**, *66*, 2201–2204.
31. Li, N.-H.; Carrera, G. M., Jr.; Anderson, D. J. *J. Med. Chem.* **1994**, *37*, 3542–3553.