Heterocycl. Commun., Vol. 17(5-6), pp. 203–205, 2011 • Copyright © by Walter de Gruyter • Berlin • Boston. DOI 10.1515/HC.2011.043

An unusual route to a quinoline 1-oxide *via* intramolecular addition of an enolate to an aromatic nitro group

Nayara Da Rocha F. Moreira[1], Tânia T. de Oliveira[2], Tanus J. Nagem[1] and Jason G. Taylor[1,*]

[1] Departamento de Química, ICEB, Universidade Federal de Ouro Preto, Campus Universitário Morro do Cruzeiro, 35400–000, Ouro Preto-MG, Brazil
[2] Departamento de Bioquímica e Biologia Celular, Universidade Federal de Viçosa, Av. P.H. Rolfs, s/n, 36571–000, Viçosa-MG, Brazil

*Corresponding author
e-mail: jason@iceb.ufop.br

Abstract

A mixture of ethyl 4-(2-nitrophenyl)butenoates undergoes an unusual intramolecular cyclisation in the presence of a catalytic amount of potassium *tert*-butoxide.

Keywords: cyclisation; enolate; intramolecular; nitro; oxide; quinoline.

Introduction

The quinoline *N*-oxide core structure can be encountered in a range of medicinal products exhibiting a diverse array of biological activity (Albrecht et al., 1980; Werbel et al., 1993; Mouaddib et al., 2000; Capraro et al., 2005; Andreev et al., 2006). We were prompted to disclose our preliminary results due to a recent publication (Okuma et al., 2010) in which an α, β-unsaturated carbonyl system similar to the substrate we are investigating (see **4/5** below) was cyclised under Lewis acidic conditions. Herein, we report a complementary approach utilising a base-induced intramolecular cyclisation of the transient: an enolate with an aryl nitro group to provide a 2-(ethoxycarbonyl)quinoline 1-oxide (**7**) in good yield.

Results and discussion

For the synthesis of the precursor leading to the quinoline 1-oxide, we were initially guided by literature procedures (Molina et al., 1996; Kambe et al., 2001), which described the preparation of an aldehyde by employing a Wittig reaction. Thus, compounds **1** and **2** were synthesised as shown in Scheme 1.

The subsequent Wittig reaction of **2** with phosphonium ylide **3** yielded a mixture of inseparable isomers **4** and **5** with an initial ratio of 4.5: 1 in favour of **4** (Scheme 2). The ratio was determined by integration of the methylene protons corresponding to each isomer in the ^{1}H NMR spectrum. The ^{1}H NMR signals of **4** were identified by comparison with the literature values (Lee et al., 2001), which allowed for deductive inference of the signals corresponding to **5**. A small portion of this substance was left under inert atmosphere for 5 days at room temperature and the sample was reanalysed by ^{1}H NMR, displaying a different distribution of isomers, with a ratio of 1:2.6 in favour of **5**. This suggests that double bond isomerisation gives **5** as the thermodynamic isomer.

To confirm unequivocally the presence of the two isomeric products, hydrogenation of the mixture to one single compound was attempted (Scheme 3).

The expected saturated aliphatic ester was not observed. Instead, a substituted indole **6** was isolated in good yield. The spectral data for **6** were identical with those reported for the compound that was obtained by using a different synthetic route (Guerrero and Miranda, 2006). Evidently, the nitro group is reduced faster than the alkene function resulting in formation of a substituted aniline from **4**, which then undergoes an intramolecular Michael addition reaction to give a cyclic precursor to **6**. The cyclisation of the isomer **5** requires a double bond migration in **5** to give **4**. Numerous similar isomerisations are known (Urones et al., 1999). The formation of indole **6** from the intermediate indoline requires a Pd-catalysed dehydrogenation reaction to take place. The highly efficient Pd-catalysed aromatisation of indolines is known (Bader et al., 1961).

By contrast, treatment of the mixture **4/5** with a catalytic amount of potassium *tert*-butoxide in ethanol (Scheme 4) gave a quinoline *N*-oxide **7**, which was readily identified by the downfield resonances characteristic of the quinoline *N*-oxide structure (Yin et al., 2007) and comparison with an authentic sample (Barczynski et al., 1974).

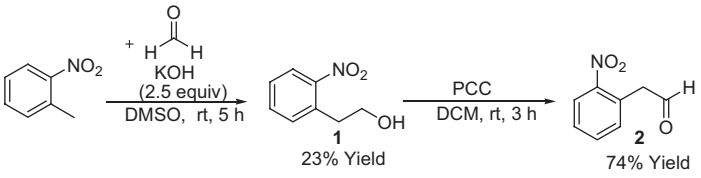
Currently, we are studying the scope, limitations and mechanism of this novel transformation that apparently involves an intramolecular addition reaction of an ester enolate to a nitro group. The results will be reported in due course.

Experimental

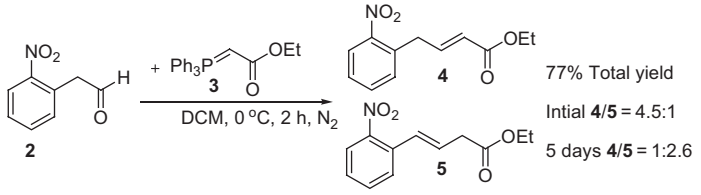
Compounds **1** (Muchowski, 1971), **2** (Noland and Sellstedt, 1966) and **3** (Kasim and Manfred, 2001; Spencer et al., 2007; Ngwendson et al., 2008) were prepared as reported previously. Compound **7** has been obtained previously by using an independent route (Barczynski et al., 1974).

Mixture of compounds 4 and 5

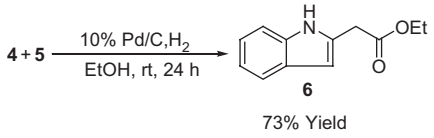
A solution of **2** (0.34 g, 1.3 mmol) in dichloromethane (15 mL) was treated dropwise over 1 h at -10°C under a nitrogen atmosphere



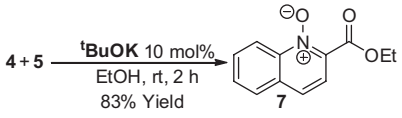
Scheme 1 Synthesis of 2-nitro-benzeneacetaldehyde.



Scheme 2 Synthesis of isomers **4** and **5** by a Wittig reaction.



Scheme 3 Domino nitro group reduction-conjugate addition-Pd-catalysed dehydrogenation reaction.



Scheme 4 Synthesis of a quinoline *N*-oxide.

with a solution of **3** (0.69 g, 1.95 mmol) in dichloromethane (15 mL). The mixture was then stirred for 2 h at 25°C and concentrated under reduced pressure. The solid residue was dissolved in hexanes (50 mL) and the mixture was stirred at 25°C for 0.5 h. The precipitate of Ph_3PO was filtered off and the filtrate was concentrated under reduced pressure. The oily residue was purified by silica gel chromatography eluting with hexanes/EtOAc (5:1) to afford a 4.5:1 ratio of **4**:**5**. The ratio changed to 1:2.6 in favour of **5** after 5 days. Compound **4** is known and its spectroscopic data are virtually identical with the reported literature values (Lee et al., 2001).

New compound 5 Pale yellow oil; $R_f = 0.3$ (silica gel, hexanes/EtOAc, 4:1); IR (neat): υ_{max} 2983, 1721, 1639, 1529, 1347, 1292, 1347, 1292, 1183, 1035, 976, 858, 787, 742, 664 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.95 (1H, d, J=7 Hz), 7.67 (1H, t, J=7 Hz), 7.36–7.45 (2H, m), 7.03 (1H, d, J=15 Hz), 6.39 (1H, dt, J=7 and 15 Hz), 4.24 (2H, q, J=7 Hz), 3.34 (2H, d, J=7 Hz), 1.31 (3H, t, J=7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 166.1, 144.9, 133.5, 132.5, 128.8, 128.2, 127.5, 124.5, 123.3, 60.9, 35.6, 14.2; EI-MS: *m/z* 235 (M^+, 5%), 190 (25%), 172 (25%), 162 (50%), 120 (100%), 116 (90%), 92 (45%), 77 (35%).

Ethyl (indol-2-yl)acetate (6) A 50-mL round-bottom flask, equipped with magnetic stir bar and rubber septum, was charged with a solution of **4** and **5** (310 mg, 1.3 mmol) in absolute ethanol (20 mL). To the solution Pd/C (10%, 100 mg) was added and the mixture was exposed to hydrogen using a balloon. The mixture was vigorously stirred overnight and then filtered through a plug of celite. The celite was rinsed with additional ethanol. The filtrate was concentrated on a rotary evaporator yielding indole 194 mg (73%) of the indole **6** as pale yellow oil; R_f=0.5 (silica gel, hexanes/EtOAc, 7:3). Spectroscopic data are virtually identical with reported values (Guerrero and Miranda, 2006).

2-(Ethoxycarbonyl)quinoline 1-oxide (7) A 50-mL round-bottom flask equipped with a magnetic stir bar was charged with a 1:2.6 mixture of **4** and **5** (100 mg, 0.43 mmol). Absolute ethanol (15 mL) was added, followed by potassium *tert*-butoxide (5 mg, 0.044 mmol) and the mixture was stirred at room temperature for 2 h. Concentration of the mixture under reduced pressure followed by silica gel chromatography (hexanes/EtOAc, 5:1) of the oily residue gave 76 mg (83%) of **7** as a pale yellow oil; R_f=0.3 (hexanes/EtOAc, 4:1); ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.82 (1H, d, J=8 Hz), 7.91 (1H, d, J=8 Hz), 7.84 (1H, t, J=8 Hz), 7.70–7.76 (2H, m), 7.61 (1H, d, J=8 Hz), 4.59 (2H, q, J=7 Hz), 1.65 (3H, t, J=7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 162.4, 142.5, 137.8, 130.9, 130.6, 129.7, 128.2, 124.7, 121.1, 120.3, 62.6, 14.2; CI-MS: *m/z* 218 ($[M+H]^+$, 100%), 202 (20%).

Acknowledgements

The authors thank the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), the Fundação Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) and the Fundação de Amparo à Pesquisa do Estado de Minas Gerais (FAPEMIG) for financial support. We thank Dr. Robson J. de Cássia FrancoAfonso and Dr. Maurício Xavier Coutrim for providing excellent mass spectrometry service.

References

Albrecht, T.; Spleelman, D. J.; Sadagopa Ramanujam, V. M.; Lund, H. W.; Legator, M. S.; Trieff, N. M. Correlation of the chemical structure of 4-nitroquinolines inactivating human cytomegalovirus and established in vivo carcinogenicity tests. *Terat. Carcin. Mut*. **1980**, *1*, 161–169.

Andreev, V. P.; Korvacheva, E. G.; Nizhnik, Y. P. Effect of pyridine and quinoline N-oxides on microsomal Na,K-ATPase activity. *Pharm. Chem. J*. **2006**, *40*, 347–348.

Bader, A. R.; Bridgwater, R. J.; Freeman, P. R. Indoles. II.1a,1b. The acid-catalyzed rearrangement of N-2-alkenylanilines. *J. Am. Chem. Soc.*, **1961**, *83*, 3319–3323.

Barczynski, P.; Brzezinski, B.; Szafran, M. Esterification of some α-carboxy *N*-oxides. *Roczniki Chem.* **1974**, *48*, 903–905.

Capraro, H.-G.; Furet, P.; Garcia-Echeverria, C.; Stauffer, F. 1H-Imidaz [4,5-C] quinoline dervivatives in the treatment of protein kinase dependent disease. WO2005054238, 2005, p. 138.

Guerrero, M. A.; Miranda, L. D. Et_3B-Mediated radical alkylation of pyrroles and indoles. *Tetrahedron Lett.* **2006**, *47*, 2517–2520.

Kambe, M.; Arai, E.; Suzuki, M.; Tokuyama, H.; Fukuyama, T. Intramolecular 1,3-dipolar cycloaddition strategy for enantioselective synthesis of FR-900482 analogues. *Org. Lett.* **2001**, *3*, 2575–2578.

Kasim, P.; Manfred, H. Syntheses of the macrocyclic spermine alkaloids (±)-budmunchiamine A–C. *Helv. Chim. Acta* **2001**, *84*, 180–186.

Lee, J. G.; Choi, K. I.; Koh, H. Y.; Kim, Y.; Kang, Y.; Cho, Y. S. Indium mediated reduction of nitro and azide groups in the presence of HCl in aqueous media. *Synthesis* **2001**, *1*, 81–84.

Molina, P.; Alajarin, M.; Sanchez-Andrada, P.; Carrio, J. S.; Martinez-Ripoll, M.; Anderson, J. E.; Jimeno, M. L.; Elguero, J. New models for the study of the racemization mechanism of carbodiimides. Synthesis and structure X-ray crystallography and ^1H NMR of cyclic carbodiimides. *J. Org. Chem.* **1996**, *61*, 4289–4299.

Mouaddib, A.; Joseph, B.; Hasnaoui, A.; Mérour, J.-Y. Synthesis of indolo[3,2-c]quinoline and pyrido [3′,2′:4,5] [3,2-*c*] quinoline derivatives. *Synthesis* **2000**, *4*, 549–556.

Muchowski, J. M. Benzodiazocines. II. The synthesis of some hexahydro-1,4-benzodiazocines. *Can. J. Chem*. **1971**, *49*, 2023–2028.

Ngwendson, J. N.; Schultze, C. M.; Bollinger, J. W.; Banerjee, A. Effect of base on alkyltriphenylphosphonium salts in polar aprotic solvents. *Can. J. Chem*. **2008**, *86*, 668–675.

Noland, W. E.; Sellstedt, J. H. A new synthesis of o-nitrophenylacetaldehyde. *J. Org. Chem*. **1966**, *31*, 345–346.

Okuma, K.; Seto, J. I.; Nagahora, N.; Shioji, K. Chemoselective synthesis of quinoline N-oxides from 3-(2-nitrophenyl)-3-hydroxypropanones. *J. Heterocycl. Chem*. **2010**, *47*, 1372.

Spencer, E. C.; Mariyatra, M. B.; Howard, J. A.; Kenwright, A. M.; Panchanatheswaran, K. The synthesis and structural characterisation of the mercury (II) halide complexes of the phosphorus ylide carbethoxymethylenetriphenylphosphorane. *J. Organomet. Chem.* **2007**, *692*, 1081–1086.

Urones, J. G.; Garrido, N. M.; Diez, D.; Dominguez, S. H.; Davies, S. G. Conjugate addition to (α, β)(α′, β′)-diendioate esters by lithium (α-methylbenzyl)benzylamide: tandem addition-cyclisation vs. double addition. *Tetrahedron: Asymmetry* **1999**, *10*, 1637–1641.

Werbel, L. M.; Kersten, S. J.; Turner, W. R. Structure-activity relationships of antimalarial indolo [3,2-c]quinolines [1, 2]. *Eur. J. Med. Chem*. **1993**, *28*, 837–852.

Yin, J.; Xiang, B.; Huffman, M. A.; Raab, C. E.; Davies, I. W. A General and efficient 2-amination of pyridines and quinolines. *J. Org. Chem.* **2007**, *72*, 4554–4557.

Received September 2, 2011; accepted November 4, 2011