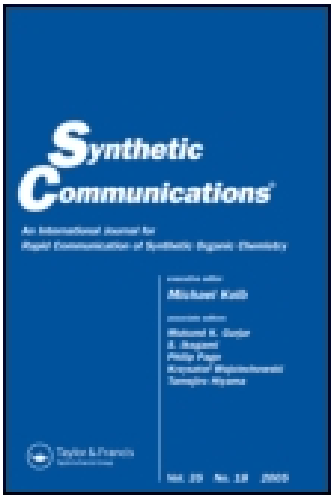

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Thermal Cleavage of Oxazolidine-4,5-diones to Imines: A Short Synthesis of 3,4-Dihydro-3,3-dimethyl-7-trifluoromethylisoquinoline-2-oxide

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Published online: 21 Aug 2006.

To cite this article: Ronald C. Bernotas , Ginette Adams & Thaddeus R. Nieduzak (1996) Thermal Cleavage of Oxazolidine-4,5-diones to Imines: A Short Synthesis of 3,4-Dihydro-3,3-dimethyl-7-trifluoromethylisoquinoline-2-oxide, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 26:18, 3471-3477, DOI: 10.1080/00397919608003751

To link to this article: http://dx.doi.org/10.1080/00397919608003751

SYNTHETIC COMMUNICATIONS, 26(18), 3471-3477 (1996)

THERMAL CLEAVAGE OF OXAZOLIDINE-4,5-DIONES TO IMINES: A SHORT SYNTHESIS OF 3,4-DIHYDRO-3,3-DIMETHYL-7-TRIFLUOROMETHYLISOQUINOLINE-2-OXIDE

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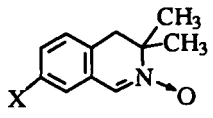
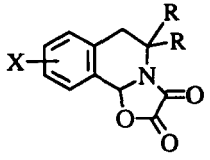
ABSTRACT: A series of oxazolidine-4,5-diones **2** was thermally cleaved to cyclic imines **3** in excellent yield. This reaction was utilized in an efficient synthesis of a 3,4-dihydroisoquinoline-based nitrone **1b**.

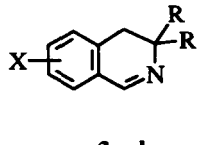
In disease states including stroke and septic shock where radicals can cause cellular damage, radical scavengers may be useful therapeutic agents.[1] As part of a project targeting one such class of radical scavengers, nitrones **1**, we synthesized intermediate imines **3** from **2**[2] using an acidic methanolysis procedure developed earlier by Merck chemists.[3] We report here an alternative conversion of **2** to **3** by simply heating **2** in the absence of any reagents and demonstrate the utility of this procedure by an efficient, high yield synthesis of nitrone **1b**.



1a X = H
1b X = CF_3



2a X = Cl, R = CH_3
2b X = CF_3, R = CH_3
2c X = H, R,R = -$(CH_2)_4$-
2d X = Cl, R,R = -$(CH_2)_5$-



3a-d

*To whom correspondence should be addressed.

Oxazolidine-4,5-diones **2** have been converted to imines **3** by heating at reflux in 5:95 concentrated sulfuric acid:methanol for 4-8 hours.[2] While this approach worked well for this ring system, the seven-membered ring (**4**) produced roughly equal amounts of desired **5** and side product **6** (Figure 1).[4] To overcome this problem, we attempted a thermal conversion of **4** to **5** by heating **4** above its melting point, which caused gas to evolve. Once gas evolution had ceased, we isolated imine **5** in excellent yield and of sufficient purity for subsequent reactions. The elimination of any reagents made the reaction setup and workup very simple.

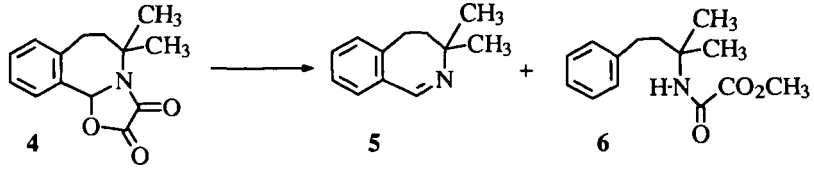


FIG. 1

To simplify the reaction conditions for the conversion of compounds **2** to **3**, we extended the same thermal conditions to oxazolidine-4,5-dione **2a**. Upon immersing a reaction vessel containing neat **2a** under nitrogen into a preheated bath, the substrate melted and evolved gas for about 15-20 minutes. The resulting liquid proved to be desired imine **3a** based on comparison to authentic material prepared by the acid methanolysis method. A proposed mechanism for this reaction involves the loss of carbon dioxide and carbon monoxide (Figure 2). The crude imine was pure by ^{1}H NMR and generally was used in the next step (reduction with $NaBH_4$) without further purification. In other examples, including spirocyclic compounds, very good to excellent yields of the 3,4-dihydroiso-

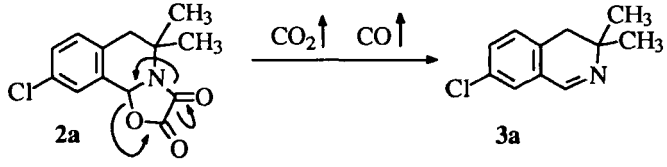
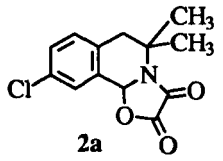
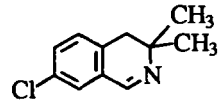
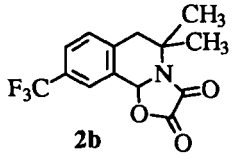
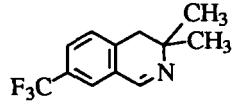
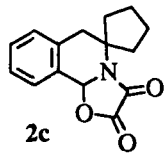
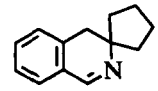
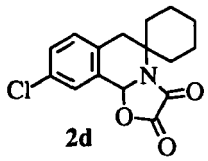
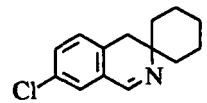


FIG. 2

TABLE 1
THERMOLYTIC CLEAVAGE OF OXAZOLIDINE-4,5-DIONES

OXAZOLIDINE-4,5-DIONE	TEMPERATURE (°C)	IMINE	YIELD (%)
 **2a**	155-160	 **3a**	97
 **2b**	150-155	 **3b**	96
 **2c**	170-175	 **3c**	100
 **2d**	170-175	 **3d**	97

quinolines were obtained from the thermolysis, demonstrating that the thermal conversion is a quick and simple alternative to the acid-based method (Table 1).[5]

The utility of this reaction has been shown by a short, efficient synthesis of nitrone **1b** (Figure 3). Alkene **7** was subjected to a Ritter reaction[6] and the resulting formamide **8** was cyclized to **2b** by treatment with oxalyl chloride in dichloromethane followed by anhydrous $FeCl_3$.[2] Oxazolidine-4,5-dione **2b** was converted thermally to imine **3b** which was then reduced with $NaBH_4$ to give

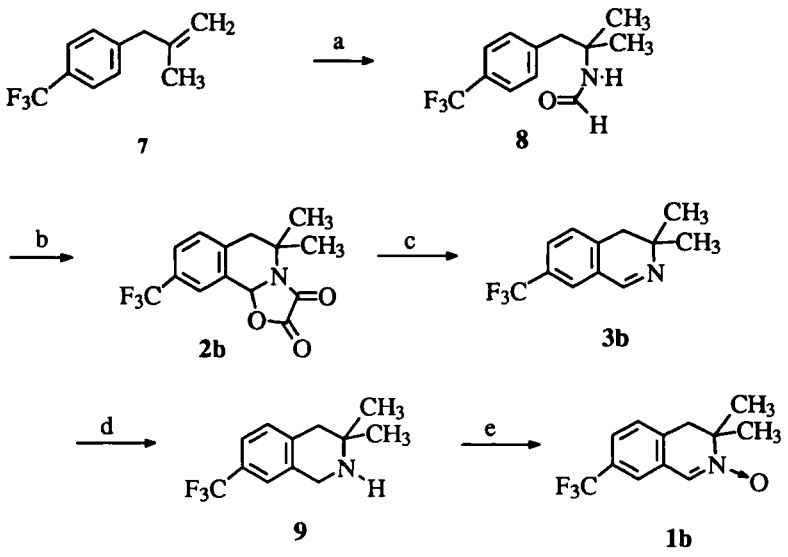


FIG. 3

a) $NaCN/H_2SO_4/CH_3CO_2H$ b) $(COCl)_2/CH_2Cl_2$, then $FeCl_3$ c) heat
d) $NaBH_4/CH_3OH$ e) $Na_2WO_4{\cdot}2H_2O/H_2O_2/H_2O/CH_3CH_2OH$

tetrahydroisoquinoline **9**. Oxidation with hydrogen peroxide using $Na_2WO_4{\cdot}2H_2O$ as a catalyst[7] afforded nitrone **1b** in 52% overall yield from alkene **7**.

In conclusion, neat oxazolidine-4,5-diones were readily converted to 3,4-dihydroisoquinolines simply by heating, eliminating the need for any additional reagents. This procedure was applied to an efficient synthesis of nitrone **1b**.

EXPERIMENTAL SECTION

Proton NMR and ^{13}C NMR were obtained on Varian XL300 and Gemini 300 spectrometers. In the proton NMR data for formamide **8**, M refers to the major isomer and m refers to the minor isomer. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Solvents were of reagent grade or anhydrous Sure-Seal grade from Aldrich Chemical Co. Ratios of ethyl acetate:hexane are abbreviated E:H.

N-Formyl-1-(4-trifluorophenyl)-2-methyl-2-aminopropane (8)

Caution! *Sodium cyanide is highly toxic and should be handled with extreme care in an efficient hood using gloves and other appropriate precautions.*

To a stirred suspension of NaCN (4.51 g, 92.0 mmol) in glacial acetic acid (45 mL) cooled in an ice bath was added a 1:1 mixture of conc H_2SO_4:acetic acid (22.4 mL). After 15 min, 3-(4-trifluromethylphenyl)-2-methyl-1-propene **7** (9.20 g, 46.0 mmol) was added and the ice bath removed. After 40 h, nitrogen was bubbled through the reaction for 1 h and then the reaction was slowly poured onto a well-stirred mixture of ice (200 g), water (100 mL), and Na_2CO_3 (75 g). Gas evolved. The now basic mixture was extracted with ether (200 ml, 100 mL) and the combined extracts washed with brine (100 mL) and dried with $MgSO_4$, filtered through Na_2SO_4, and concentrated *in vacuo* to a thick orange oil. This was chromatographed using 50:50, then 100:0 E:H to afford 8.42 g (75%) of the desired product (R_f ~ 0.3 in first system) as a viscous, clear, slightly yellow liquid. Anal. Calc. for $C_{12}H_{14}F_3NO$: C 58.77, H 5.75, N 5.71. Found: C 58.84, H 5.97, N 5.47. ^{1}H NMR ($CDCl_3$): 8.08 (1H, M+m, dd, J = 12.0, 1.9 Hz), 7.57 (2H, M+m, m), 7.28 (2H, M+m, m), 5.73 (1H, m, bd), 5.06 (1H, M, bs), 3.16 (2H, M, s), 2.86 (2H, m, s), 1.37 (6H, M, s), 1.36 (6H, m, s) ppm. ^{13}C NMR ($CDCl_3$): 162.71, 160.82, 141.72, 140.08, 130.90, 130.77, 125.30, 125.26, 124.94, 124.90, 124.85, 124.80, 54.23, 52.96, 49.86, 44.41, 28.40, 27.46 ppm. ^{19}F NMR ($CDCl_3$): -62.92, -63.04 ppm. IR (neat): 1676, 1327, 1165, 1124 cm^{-1}. CIMS (CH_4): 246 (94%), 226 (78%), 86 (100%).

Oxazolidine-4,5-dione (2b)

To a solution of formamide **8** (8.35 g, 34.0 mmol) in CH_2Cl_2 (340 mL) was added oxalyl chloride (3.26 mL, 37.4 mmol). Gas evolved. After 1 h, the reaction was cooled in an ice bath and treated with anhydrous $FeCl_3$ (6.62 g, 40.8 mmol). The reaction was allowed to warm to rt as the ice melted. After 16 h, the reaction was treated with 2M hydrochloric acid (340 mL), stirred 1 h and the layers separated. The aqueous was extracted with CH_2Cl_2 (100 mL) and the combined organics dried (Na_2SO_4) and concentrated *in vacuo* to a viscous, foaming oil. This was

dissolved in hot 30:70 E:H (~75 mL) and product rapidly crystallized out. Hexanes (~75 mL) were added to maximize recovery. Suction filtration, with hexane washes, yielded a white crystalline solid (8.42 g, 83%). Mt. pt.: 123.5-124.5°C. Anal. Calc. for $C_{14}H_{12}F_3NO_3$: C 56.19, H 4.04, N 4.68. Found: C 56.42, H 4.07, N 4.65. ^{1}H NMR ($CDCl_3$): 7.77 (1H, s), 7.71 (1H, d, J = 8.2 Hz), 7.44 (1H, d, J = 7.7 Hz), 6.42 (1H, s), 2.99 (2H, m), 1.77 (3H, s), 1.39 (3H, s) ppm. ^{13}C NMR ($CDCl_3$): 158.66, 150.49, 137.08, 132.69, 130.58, 130.14, 128.87, 126.80, 126,75, 126.70, 126.65, 125.37, 121.75, 119.74, 119.68, 119.63, 119.59, 81.36, 56.28, 42.37, 26.29, 24.14 ppm. ^{19}F NMR ($CDCl_3$): -63.09 ppm IR (KBr): 1716, 1417, 1332, 1143, 1122 cm^{-1}. CIMS (CH_4): 317 (100%).

*7-Trifluoromethyl-3,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (**9**)*

Oxazolidine-4,5-dione **1b** (2.99 g, 10.0 mmol) stirred in a flask was immersed in a preheated oil bath (bath temperature 155-160°C). The compound melted and gas evolved. After 30 min, gas evolution had ceased. The reaction was allowed to cool, then treated with methanol (20 mL) and then, carefully, with $NaBH_4$ (0.38 mmol). Gas and heat evolved. After 16 h, 1M aqueous NaOH (20 mL) was added to the reaction. After 20 min, the reaction was diluted with water (50 mL), extracted with CH_2Cl_2 (2 x 50 mL) and the extracts dried with Na_2SO_4 and concentrated *in vacuo*. The resultant oil was chromatographed eluting with 0:100, then 20:80 EtOH:E isolating the component with an R_f ~ 0.1 in the initial system. The product oil was briefly heated under vacuum to remove residual solvent; on cooling the title compound was isolated as an off-white solid (2.10 g, 92% for two steps). Mt. pt.: 41-42°C. Anal. Calc. for $C_{12}H_{14}F_3N$: C 62.87, H 6.16, N 6.11. Found: C 62.95, H 6.13, N 6.13. ^{1}H NMR ($CDCl_3$): 7.73 (1H, s), 7.52 (1H, bm), 7.34 (1H, bs), 7.31 (1H, bs), 3.14 (2H, s), 1.47 (6H, s) ppm. ^{13}C NMR ($CDCl_3$): 133.42, 131.28, 130.40, 129.96, 129.15, 128.03, 125.34, 125.30, 125.25, 121.06, 121.01, 120.96, 67.23, 41.65, 24.71 ppm. ^{19}F NMR ($CDCl_3$): -63.32 ppm. IR (KBr): 1325, 1242, 1169, 1126 cm^{-1}. CIMS (CH_4): 244 (100%).

*7-Trifluoromethyl-3,3-dimethyl-3,4-dihydroisoquinoline-2-oxide (**1b**)*

To a solution of amine **9** (2.00 g, 8.72 mL) in ethanol (20 mL) was added a

solution of Na_2WO_4 dihydrate (0.14 g, 0.44 mmol) in water (10 mL) followed by 30% aqueous H_2O_2 (2.2 mL, 22 mmol). More oxidant (1.0 mL) was added after 1 h and another portion (0.5 mL) 0.5 h later. After 2 h of reaction time, TLC showed virtually no starting material so the reaction was diluted with water (70 mL) and extracted with CH_2Cl_2 (100 mL, 50 mL). The combined extracts were dried with Na_2SO_4, concentrated in vacuo, and chromatographed with ethyl acetate to afford an oil (R_f ~ 0.6). The oil was carefully "triturated" with hexanes and reconcentrated to give **5** as a waxy solid (1.95 g, 92%). Mt. pt.: 51.5-53.0°C. Anal. Calc. for $C_{12}H_{12}F_3NO$: C 59.26, H 4.97, N 5.76. Found: C 59.10, H 5.04, N 5.73. ^{1}H NMR ($CDCl_3$): 7.38 (1H, bd, J = 8.2 Hz), 7.30 (1H, bs), 7.16 (1H, bd, J = 8.2 Hz), 4.09 (2H, s), 2.68 (2H, s), 1.19 (6h, s) ppm. ^{13}C NMR ($CDCl_3$): 138.69, 138.71, 135.22, 129.98, 128.27, 127.85, 126.08, 122.80, 122.75, 122.70, 122.67, 122.62, 122.57, 122.47, 48.63, 44.26, 41.52, 27.62 ppm. ^{19}F NMR ($CDCl_3$): -62.87 ppm. IR (KBr): 1331, 1184, 1161, 1119 cm^{-1}. CIMS (CH_4): 230 (100%).

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(Received in the USA 14 April 1996)