Pergamon

Tetrahedron Letters 41 (2000) 3035–3038

TETRAHEDRON LETTERS

Intramolecular radical acylation of 2-methylsulfonylpyrroles

Luis D. Miranda,[a,*] Raymundo Cruz-Almanza,[a,*] Abraham Alvarez-García[b] and Joseph M. Muchowski[c]

[a]*Instituto de Química, Universidad Nacional Autónoma de México, Circuito Exterior, Ciudad Universitaria Coyoacan, Coyoacan D. F. 04510, Mexico*

[b]*Facultad de Química, Universidad Autónoma del Estado de México, Toluca Edo. de Méx. 05000, Mexico*

[c]*Roche Bioscience, 3401 Hillview Ave., Palo Alto, CA 94304-1320, USA*

Received 26 January 2000; accepted 24 February 2000

Abstract

Primary alkyl radicals generated (AIBN/Bu_3SnH) from 1-(2- or 3-haloalkyl)-2-methylsulfonylpyrroles are intercepted by CO (80 atm), and the acyl radicals so produced undergo intramolecular oxidative cyclization at the α-position, giving bicyclic ketones with retention or loss of the sulfonyl moiety.

Keywords: acylation; acyl radical; carbonylation; pyrroles; pyrrolizidones; indolizidinones.

Radical carbonylation is a useful procedure for constructing asymmetric ketones when the carbonylation process is coupled with the inter- or intramolecular addition of the acyl radical to a double bond.[1] Recently, we reported a process in which such a radical carbonylation was combined with an intramolecular addition onto indole and pyrrole systems.[2] It is well known that systems bearing a sulfone group are excellent radical acceptors[3a] and undergo formal radical aromatic substitutions in which the sulfone group is usually, although not always, lost.[3b–g] Also, the addition step may, or may not, occur at the *ipso* position.[3g] We describe herein our recent findings on the radical carbonylation and cyclization of the N-2 and 3-haloalkyl-2-methylsulfonylpyrroles **1** (Scheme 1).

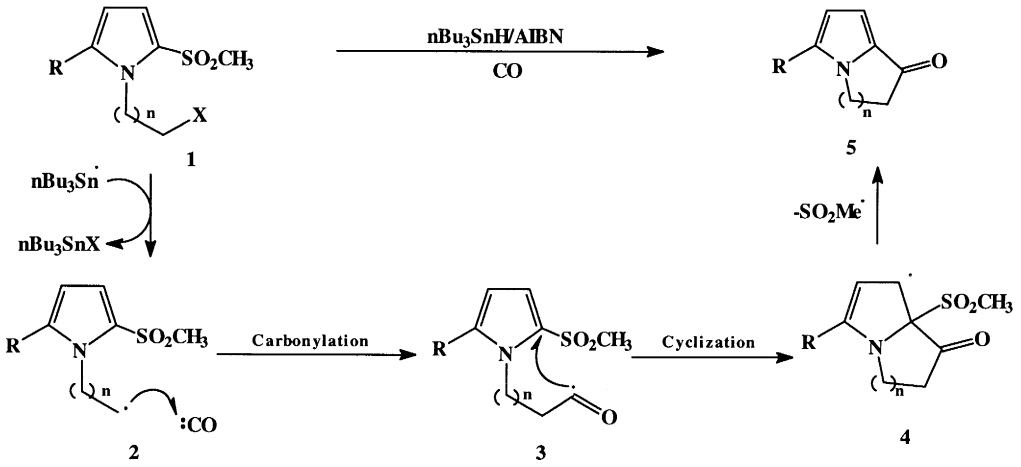
The AIBN/Bu_3SnH-mediated radical reaction of **1** with CO was examined with the expectation that the acyl radical **3**, derived from **2**, would add intramolecularly to C-2 of the heteroaromatic system giving **4**, which, upon aromatization by loss of the methylsulfonyl radical, would produce the bicyclic ketone **5**.

The required methylsulfonylpyrrole derivatives were synthesized as reported before from known 2-methylthiopyrrole[4] (**6**) which was acylated under Vilsmeier–Haack conditions and oxidized to the corresponding sulfone (Scheme 2). The sulfones were alkylated with the appropriate dihaloalkane.

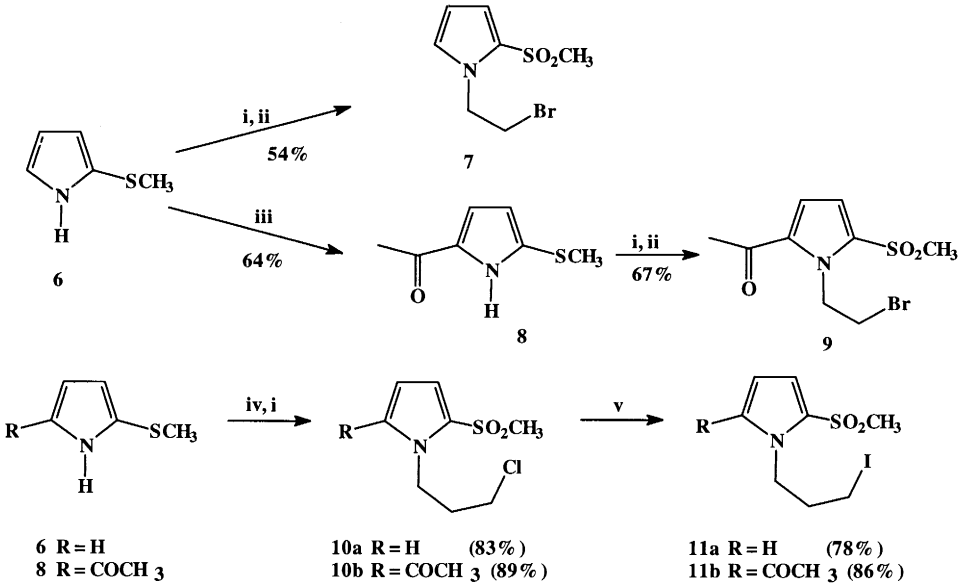
The methylsulfonylpyrroles were subjected to standard radical carbonylation conditions,[2,5] i.e. 0.02 M benzene solution of the substrate, at 95°C under CO pressure (80 atm), portionwise addition of

* Corresponding author. Tel: 52 56 22 44 28; fax: 52 56 16 22 17; e-mail: raymundo@servidor.unam.mx (R. Cruz-Almanza)

0040-4039/00/$ - see front matter
PII: S0040-4039(00)00342-7

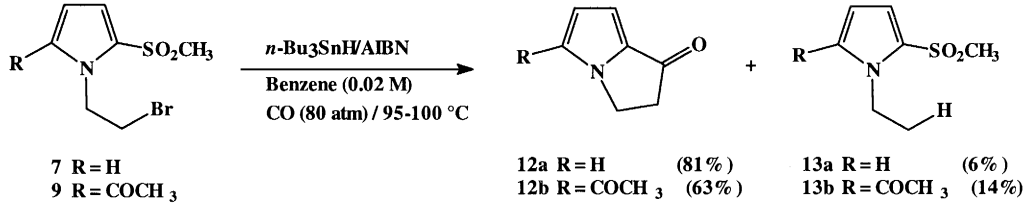


Scheme 1.



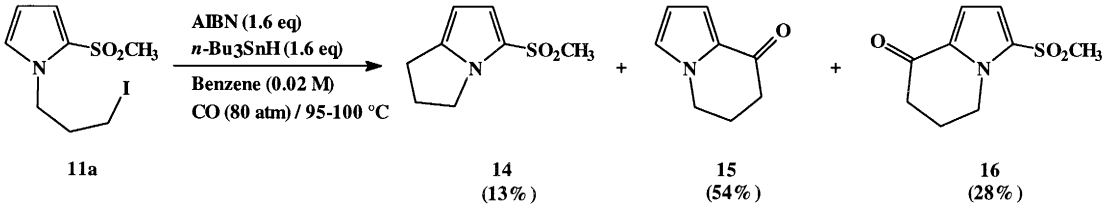
Scheme 2. Conditions: (i) MCPBA, dichloromethane, 0°C; (ii) 1,2-dibromoethane, NaH, DMF, 0°C; (iii) $POCl_3$, *N*-acetylmorpholine, 2 h, then AcONa aq. 3 h; (iv) 1-bromo-3-chloropropane, NaH, DMF, 0°C; (v) NaI, CH_3CN reflux 26 h

Bu_3SnH/AIBN at 1 h intervals.[2] Under such conditions, compound **7** gave the expected pyrrolizidone **12a**[5] in good yield, and a small amount of the reductive dehalogenation product **13a**. When the 5-acyl compound **9** was submitted to the same reaction conditions (five additions/0.4 equiv.) the diketone **12b** and reduction product **13b** were obtained in moderate and low yield, respectively (Eq. (1)).



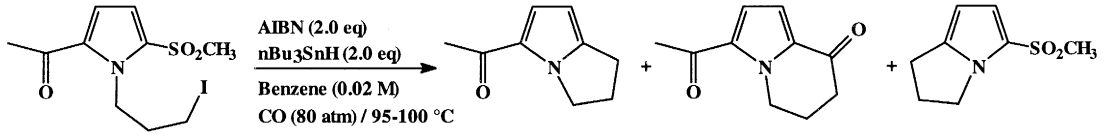
(1)

The homologous compound **11a** also gave the expected indolizidinone **15** in moderate yield and the pyrrolizidine **14**, resulting from competitive 5-exo cyclization of the alkyl radical, in low yield (Eq. (2)). The formation of **16**, the product derived from radical attack at C-5, is interesting, and has precedence in oxidative intramolecular radical alkylation of **11a** and related compounds.[3a]



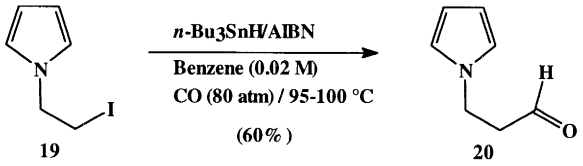
11a → **14** (13%) + **15** (54%) + **16** (28%) (2)

When pyrrole **11b** was subjected to the usual reaction conditions, **17** was obtained as the major product. The desired diketone **18** was isolated in very low yield together with a small amount of the unexpected sulfone **14** (Eq. (3)). This compound is formed by alkyl radical addition at C-5, and subsequent aromatization by the interesting loss of an acetyl radical. When **11b** was reacted with *n*-Bu_3SnH/AIBN in the absence of CO, **17** and **14** were isolated in 74 and 23% yields, respectively.



11b → **17** (81%) + **18** (7%) + **14** (11%) (3)

Finally, it is noteworthy that 1-(2-iodoethyl)pyrrole **19**, under the usual radical carbonylation conditions, gave 3-(1-pyrrolyl)propionaldehyde **20** (60%), and no **12a**, a result which is not surprising given that the electronically analogous alkyl radicals fail to add to pyrroles not activated by one or more electron attracting substituents.[3a]



19 → **20** (4)

In conclusion, four different methylsulfonylpyrrole derivatives were studied in a tandem carbonylation/cyclization radical process. The methodology described herein is of interest since pyrrolizidones and indolizidinones were synthesized by a novel process, usually in good to moderate yields.

Acknowledgements

Financial support from CONACYT (No. 27997E) is gratefully acknowledged. We also wish to thank R. Patiño, J. Pérez, W. Matus and H. Rios for technical support.

References

1. (a) Ryu, I.; Sonoda, N. *Angew. Chem., Int. Ed. Engl*. **1996**, *35*, 1050–1066. (b) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.*, **1996**, *96*, 177–194.

2. Miranda, L. D.; Cruz-Almanza, R.; Pavón, M.; Alva, E.; Muchowski, J. M. *Tetrahedron Lett.* **1999**, *40*, 7153–7157.
3. (a) Ryu, I.; Kuriyama, H.; Minakata, S.; Komatsu, M.; Yoon, J.-Y.; Kim, S. *J. Am. Chem. Soc.* **1999**, *121*, 12190. (b) Caddick, S.; Aboutayab, K.; West, R. I. *J. Chem. Soc., Chem. Commun*. **1995**, 1353–1354. (c) Caddick, S.; Aboutayab, K.; Jenkins, K.; West, R. I. *J. Chem. Soc., Perkin Trans. 1* **1996**, 675–682. (d) Caddick, S.; Aboutayab, K.; West, R. I. *Synlett* **1993**, 231–232. (e) Aldabbagh, F.; Bowman, R. *Tetrahedron Lett.* **1997**, *21*, 3793–3794. (f) Aldabbagh, F.; Bowman, R. *Tetrahedron* **1999**, *55*, 4109–4122. (g) Antonio, Y.; De la Cruz, E.; Galeazzi, E.; Guzman, A.; Bray, B. L.; Greenhouse, R.; Kurz, L. J.; Lusting, D. A.; Maddox, M. L.; Muchowski, J. M. *Can. J. Chem*. **1994**, *72*, 15
4. Franco, F.; Greenhouse, R.; Muchowski, J. M. *J. Org. Chem.* **1982**, *47*, 1682–1988.
5. *Typical procedure*: A benzene solution 0.02 M of methylsulfonylpyrrole (1 equiv.), *n*-Bu_3SnH (0.4 equiv.) and AIBN (0.4 equiv.) under 80 atm of CO was heated at 95–100°C for 1 h. After this time the autoclave was cooled to room temperature and another 0.4 equiv. of *n*-Bu_3SnH and 0.4 equiv. of AIBN was added, and heated at 95–100° for 1 h under 80 atm of CO. This process was repeated until no starting material was present. The reaction was monitored by TLC analysis. The autoclave was cooled and the solvent removed under reduced pressure and the residue partitioned between hexane and acetonitrile. The polar layer was washed with hexane (five times). After, the solvent was evaporated and the crude product was purified by flash column chromatography (Hex-EtOAc*).* Selected spectral data of final products: compound **12a**: IR ($CHCl_3$):ν_{max} (cm^{-1}) 1695.4, 2925.9, 2958.7; ^1H NMR ($CDCl_3$, 300 MHz): δ 3.09 (t, 2H, *J*=6.3 Hz), 4.31 (t, 2H, *J*=6.3 Hz), 6.52 (dd, 1H, $J_{7,6}$=4.05, $J_{6,5}$=2.25 Hz), 6.73 (dd, 1H, $J_{7.6}$=4.05, $J_{7,5}$=1.05 Hz), 7.04 (dd, 1H, $J_{7,5}$=1.05, $J_{6,5}$=2.25 Hz); EM (IE) *m/z*: M^+=121 (100%). Compound **14**: IR ($CHCl_3$):ν_{max} (cm^{-1}) 1153.3, 1315.4, 2854.5, 2927.8, 2958.7; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.56 (q, 2H, *J*=7.25 Hz), 2.88 (t, 2H, *J*=7.4 Hz), 3.07 (s, 3H), 4.19 (t, 2H, *J*=7.14 Hz), 5.92 (d, 1H, *J*=3.89 Hz), 6.87 (d, 1H, *J*=3.89 Hz); EM (IE) *m/z*: M^+=185 (100%). Compound **15**: IR ($CHCl_3$):ν_{max} (cm^{-1}) 1694.8, 2856.4, 2889.2, 2873.8, 2931.7, 2962.5; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.28 (q, 2H, *J*=6.0 Hz), 2.6 (t, 2H, *J*=6.35 Hz), 4.12 (t, 2H, *J*=5.84 Hz), 6.26 (dd, 1H, $J_{8,7}$=4.1, $J_{7,6}$=2.38 Hz), 6.86 (dd, 1H, $J_{7.6}$=2.38, $J_{8.6}$=1.56 Hz), 7.02 (dd, 1H, $J_{8,7}$=4.1, $J_{8,6}$=1.56 Hz); EM (IE) *m/z*: M^+=135 (100%). Compound **16** IR ($CHCl_3$):ν_{max} (cm^{-1}) 1110.9, 1334.7, 1694.8, 2856.4, 2927.8, 2960.6; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.37 (q, 2H, *J*=6.22 Hz), 2.67 (s, 3H), 2.67 (t, 2H, *J*=6.15 Hz), 3.16 (s, 3H), 4.47 (t, 2H, *J*=5.85 Hz), 6.92 (d, 1H, *J*=4.2 Hz), 7.0 (d, 1H, *J*=4.2 Hz). EM: M^+ m/z=213 (100%). Compound **12b**: IR ($CHCl_3$):ν_{max} (cm^{-1}) 1645.8, 1695.4, 2925.9, 2958.7; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.50 (s, 3H,), 3.09 (t, 3H, *J*=5.85 Hz), 4.61 (t, 2H, *J*=5.85 Hz), 6.69 (d, 1H, *J*=4.5 Hz), 7.06 (d, 1H, *J*=4.5 Hz); EM (IE) *m/z*: M^+=163 (100%). Compound **17**: IR ($CHCl_3$):ν_{max} (cm^{-1}) 1637.4, 2854.5, 2927.8, 2960.6; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.50 (q, 2H, *J*=7.35 Hz), 2.36 (s, 3H), 2.83 (t, 2H, *J*=7.2 Hz), 4.29 (t, 2H, *J*=7.05 Hz), 5.88 (d, 1H, *J*=3.89 Hz), 6.92 (d, 1H, *J*=3.89 Hz); EM (IE) *m/z*: M^+=149 (60%). Compound **18**: IR ($CHCl_3$):ν_{max} (cm^{-1}) 1638.4, 1662.6, 2856.4, 2927.8, 2960.6; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.28 (q, 2H, *J*=6.43 Hz), 2.51 (s, 3H), 2.64 (t, 2H, *J*=6.22 Hz), 4.58 (t, 2H, *J*=5.89 Hz), 6.93 (d, 1H, *J*=4.38 Hz), 6.97 (d, 1H, *J*=4.38 Hz); EM (IE) *m/z*: M^+=177 (95%).