Reaction of 1-Substituted 2,2-Dimethyl-3-phenylpropane with *t*-BuOK in DMSO. An Unexpected Formation of a Cyclopropane Ring

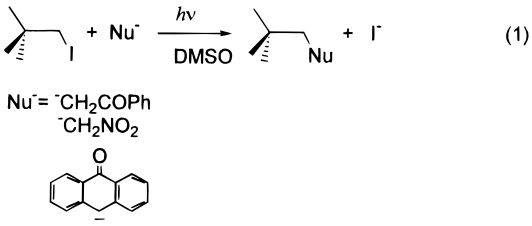
Juan E. Argüello, Alicia B. Peñéñory,* and Roberto A. Rossi*

INFIQC, Departamento de Química Orgánica, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, 5000 Córdoba, Argentina

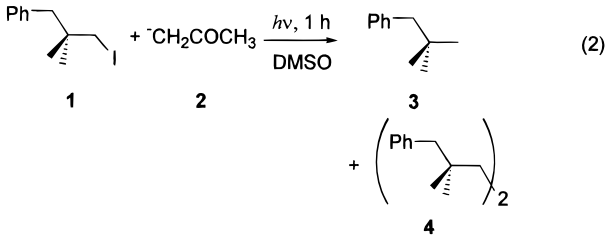
Received March 23, 1999

Neopentyl derivatives, which are very unreactive substrates in polar nucleophilic substitution,[1] have been proposed to react with different nucleophiles by an ET process in a cage collapse[2] or a chain mechanism (or $S_{RN}1$) giving the substitution products.[3]

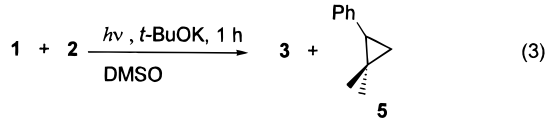
Several carbanions failed to react in liquid ammonia. In DMSO, neopentyl iodide reacts with carbanions such as the enolate anion of acetophenone, anthrone, and nitromethane anion with good yields of substitution (eq 1).[4]



With the enolate ion of acetone, neopentyl iodide gives only 100% of dehalogenation, and no substitution products were found. In the photostimulated reaction of 1-iodo-2,2-dimethyl-3-phenylpropane (**1**) with the enolate ion of acetone (**2**), only reduction **3** (50%) or dimerization **4** (20%) products of the radical intermediate are observed (eq 2).This was ascribed to the lower reactivity of the nucleophile in the coupling reaction with the neopentyl radical.

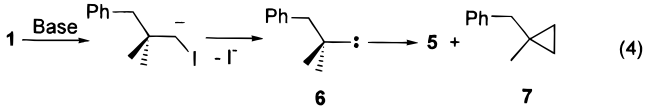


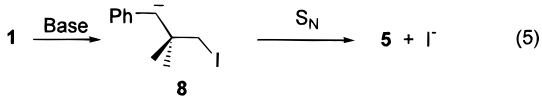
When we performed this reaction with **2** with an excess of *t*-BuOK, besides the reduction product **3**, 1,1-dimethyl-2-phenylcyclopropane **5** was formed (eq 3).



The ring-closure product **5** was not observed in the reaction with ketone enolate ions without *t*-BuOK in excess. The pK_a of *t*-BuOH is 32.2 in DMSO,[5] much higher than acetone (26.5)[5] and acetophenone (24.7);[5] meanwhile, the value for a benzylic or α-iodoalkyl is around 40.[5] In the reaction of 6-iodo-5,5-dimethyl-1-hexene with the strong base LDA, the formation of a carbene intermediate has been reported, yielding C−H insertion and addition to the double-bond products. This reaction occurred simultaneously with an ET pathway.[6]

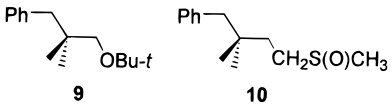
Product **5** can proceed from two possible competitive mechanisms:[7] (i) deprotonation of the α hydrogen of carbon 1 and subsequent loss of halide ion leads to the carbene **6**, which affords the insertion products **5** and **7** (eq 4); (ii) deprotonation of the benzylic carbon gives the carbanion **8,** which, by an intramolecular nucleophilic substitution, gives product **5** (eq 5).





To establish the mechanism of the formation of **5**, we studied the reaction of 1-substituted 2,2-dimethyl-3-phenylpropane with *t*-BuOK in DMSO.

Effect of the Leaving Group. The reaction of 1-iodo-2,2-dimethyl-3-phenylpropane (**1**) with *t*-BuOK in a 1:3 ratio gives 52% of dehalogenation and 46% of **5** after 30 min. The formation of **5** was 87% after 2 h of reaction at 50 °C (Table 1, entries 1 and 2). In these reactions, two minor products **9** and **10** are formed, presumably coming from an S_N2 reaction of **1** with *t*-BuOK and dimsyl anion.



With the chloride derivative **11**, 6 h were needed to yield **5** in 63% yield (Table 1, entry 3). When the leaving group was tosylate (**12**) and the reaction mixture after 30 min quenched with methyl iodide, only 2% of **5** was

* To whom correspondence should be addressed. Fax: 54-351-433-3030. E-mail: rossi@dqo.fcq.unc.edu.ar.

(1) March, J. *Advanced Organic Chemistry*, 4th ed.; John Wiley & Sons: New York, 1992.

(2) (a) Ashby, E. C.; Argyropoulus J. N. *J. Org. Chem.* **1985**, *50*, 3274. (b) Ashby, E. C.; Gurumurthy, R.; Ridlehuber, R. W. *J. Org. Chem.* **1993**, *58*, 5832.

(3) (a) Pierini, A. B.; Peñéñory, A. B.; Rossi, R. A. *J. Org. Chem.* **1985**, *50*, 2739. (b) Bornancini, E. R. N.; Palacios, S. M.; Peñéñory, A. B.; Rossi, R. A. *J. Phys. Org. Chem.* **1989**, *2*, 255.

(4) Peñéñory, A. B.; Rossi, R. A. *Gazz. Chim. Ital.* **1995**, *125*, 1.

(5) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456.

(6) Ashby, E. C.; Park, B.; Patil, G. S.; Gadru, K.; Gurumurthy, R. *J. Org. Chem.* **1993**, *58*, 424.

(7) It is known that cyclizations to small rings have an entropy advantage. Ab initio calculations demonstrate that although three-membered rings have high ring strain, the enthalpic barrier to forming them can be very small. Gronert, S.; Azizian, K.; Friedman, M. A. *J. Am. Chem. Soc.* **1998**, *120*, 3220 and references therein.

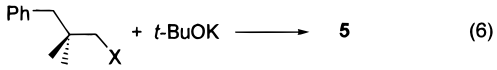
10.1021/jo9905165 CCC: $18.00
Published on Web 07/16/1999

Table 1. Reactions of Neopentyl Derivatives with *t*-BuOK in DMSO[a]

entry	substrate	time, h	convn[b] (%)	products[c] (%)
1	**1**	0.5	52.1	**5** (46.1), **9** (3.4), **10** (4.0)
2	**1**	2.0	95.2	**5** (87.2), **9** (5.9), **10** (3.0)
3	**11**	6.0	64.0	**5** (63.0)
4	**12**	0.5[d]	*e*	**5** (2.0)[f,g]
5	**13**	0.5	64.2	**5** (10.0)[h], **9**[i]
6	**13**	*j*	0	
7	**14a**	72.0	0	
8	**14b**	0.5	28.6	**16** (16.1), **17** (10.5)

[a] Performed under nitrogen atmosphere and protected from incident light; 0.04 M solutions of substrate and 0.12 M of *t*-BuOK were used. [b] Conversion determined by quantification of the halide ions by potentiometric titration with $AgNO_3$ (0.1 M) or quantification of unreacted substrate by gas−liquid chromatography. [c] The reaction products **5**, **9**, **10**, **16**, and **17** were quantified by gas−liquid chromatography using the internal standard method, error 5%. [d] Quenched with methyl iodide. [e] Undetermined. [f] The reaction develops a dark green color. [g] Together with neopentyl *p*-ethylbenzenesulfonate derivative. [h] Together with 53.8% of 2,2-dimethyl-3-phenylpropan-1-ol. [i] Not quantified. [j] A solution of substrate, without *t*-BuOK, was treated with diethyl ether and water and extracted. The substrate was recovered unchanged.

quantified together with products coming from methylation on the methyl group of the phenyl ring (Table 1, entry 4). To avoid deprotonation of the methyl group, benzenesulfonate **13** was used as leaving group instead of tosylate. Thus, the reaction **13** gives 10% of **5** with 53.8% of 2,2-dimethyl-3-phenylpropan-1-ol. As control experiments, a solution of the sulfonate **13** in DMSO was treated with diethyl ether and water the same as during the workup of the reactions. After the extraction, sulfonate **13** was recovered without changes (Table 1, entries 5 and 6).

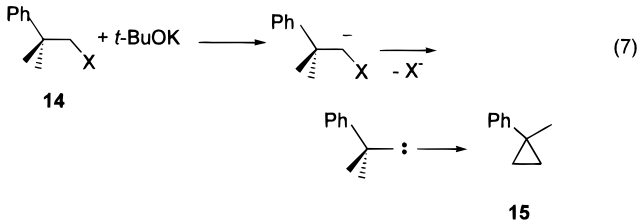


(6)

11 X = Cl
12 X = *p*-$SO_3C_6H_4CH_3$
13 X = $SO_3C_6H_5$

The effect of the leaving group I > $SO_3C_6H_5$ > Cl on the reactivity for this series of substrates is expected for a polar reaction.[8] The sulfonates showed a lower reactivity than the iodide, probably due to a competitive hydrolysis reaction in the presence of *t*-BuOK.[9]

Effect of the Substrate Structure. To test which methylenic hydrogen is involved in the formation of the cyclopropane, we studied the reactivity of the neophyl derivatives. For these substrates with no benzylic hydrogen, the mechanism of eq 5 is not possible, and the cyclopropane derivative **15** would be formed if a carbene were an intermediate (eq 7).



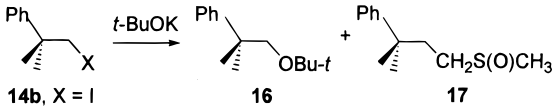
(7)

Table 2. Effect of the Trapping Agent on the Reactions of 1 with *t*-BuOK in DMSO[a]

entry	reaction conditions [**1**]/[*t*-BuOK]/[trapping agent]	convn[b] (%)	products[c] (%) **5**	**9**	**10**
1	[**1**]/[*t*-BuOK], 1:5	76.8	69.5	4.6	5
2	[**1**]/[*t*-BuOK]/[*t*-$BuNH_2$], 1:5:5	71.4	65.9	4.3	4.3
3	[**1**]/[*t*-BuOK]/[*t*-BuOH], 1:5:5	31.4	30.9	3.1	
4	[**1**]/[*t*-BuOK], 1:3, DMSO-d_6	*d*	*e*, *f*	*e*	*e*
5	[**1**]/[*t*-BuOK]/[*t*-BuOD], 1:3:3, DMSO-d_6	*d*	6.7[g]		

[a] Performed under nitrogen atmosphere and protected from incident light, reaction time 30 min. [b] Conversion determined by quantification of the halide ions by potentiometric titration with $AgNO_3$ (0.1 M). [c] The reaction products **5**, **9**, and **10** were quantified by gas−liquid chromatography, using the internal standard method, error 5%. [d] The reactions were performed in 1.0 mL of DMSO-d_6, and the halide ions were not quantified. [e] Not quantified. [f] No incorporation of deuterium was detected in **1** and **5** by GC−mass spectrometry. [g] 11% of deuterium incorporation was determined in the substrate by GC−mass spectrometry.

When a mixture of 1-chloro-2-methyl-2-phenylpropane (neophyl chloride, **14a**, X = Cl) and *t*-BuOK was stirred during 3 days, no products were found. With the iodide derivative (**14b**, X = I), only products coming from a classical nucleophilic substitution with *t*-BuOK and dimsyl anion were observed (Table 1, entries 7 and 8).

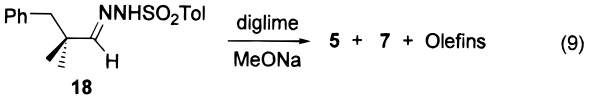


(8)

14b, X = I **16** **17**

Not even traces of the cyclopropane derivative (**15**) were detected in these two reactions; however, the formation of a carbene intermediate is more probable in the chloride derivative due to the higher inductive effect of the chloride than the iodide ion.

The carbene intermediate **6** was generated by an alternative pathway, that is, thermal decomposition of the corresponding tosylhydrazone **18** derived from the 2,2-dimethyl-3-phenylpropanal.[10] In this reaction, **5** and **7** are observed as minor products, with a complex mixture of alkenes, coming from migration of the methyl or benzyl group in the carbene intermediate (eq 9). Similar results were reported by Kirmse et al. under almost identical reaction conditions.[10]



(9)

18

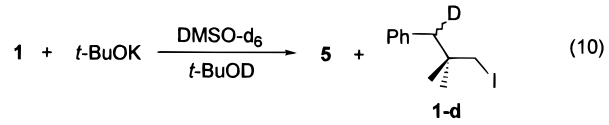
Both results (reactivity of **14** and the products coming from the carbene intermediate generated from **18**) allowed us to discard the intermediacy of a carbene in the formation of **5** (eq 4).

Effects of Labeled Solvent and Trapping Agents. The reaction of **1** with *t*-BuOK in a 1:5 ratio gives after 30 min 77% of dehalogenation and the products **5** (69.5%), **9** (4.6%), and **10** (5.0%) (Table 2, entry 1). To test the intermediacy of a carbanion, this reaction was conducted in the presence of *tert*-butylamine, a well-known trapping agent for these intermediates,[11] in a 1:5:5 ratio (**1**/*t*-BuOK/*t*-$BuNH_2$). The product distribution and yields

(8) March, J. *Advanced Organic Chemistry*, 4th ed.; John Wiley & Sons: New York, 1992; Table 10.10, p 357.
(9) Bunnett, J. F.; Basset, J. Y. *J. Am. Chem. Soc.* **1959**, *81*, 2104.
(10) Kirmse, W.; Schladetsch, H. J.; Bücking, H-W. *Chem. Ber.* **1966**, 99, 2579.
(11) Smith, G. F.; Kuivila, H. G.; Simon, R.; Sultan, L. *J. Am. Chem. Soc.* **1981**, *103*, 833.

observed were almost the same (Table 2, entry 2). When the more acidic *t*-BuOH (pK_a 32.2) was used (1:5:5 ratio), the yield of **5** was significantly depressed to 30.9% (Table 2, entry 3).

When the reaction of **1** with *t*-BuOK was performed in DMSO-d_6 for 30 min and the anions neutralized with D_2O, no incorporation of deuterium was detected in **1** and **5** by GC−mass spectrometry. The only products observed were **5**, **9**, and **10**. In the presence of *t*-BuOK and an equimolar amount of *t*-BuOD, the yield of **5** decreased to 6.7%, and 11% deuterium incorporation was observed for the substrate, affording **1**−**d.** No other products were detected (Table 2, entries 4 and 5).



These results can be rationalized as follows. The very weak acids *t*-BuNH_2 (pK_a above 35)[5] and DMSO (pK_a = 35)[5] are not able to protonate the carbanion intermediate **8**, whereas when *t*-BuOH is used, **8** is quenched and the yield of **5** decreases (thus, the pK_a for the benzylic hydrogen should be intermediate between the pK_a of *t*-BuOH (32.2) and DMSO (35)). The intermediacy of a carbanion in the formation of **5** (eq 5) is confirmed by the incorporation of deuterium in the substrate (11% d_1) in the reaction carried out in the presence of the labeled *t*-BuOD and DMSO-d_6.

Experimental Section

Materials. 1-Iodo-2,2-dimethyl-3-phenylpropane[12] (**1**) and 1-chloro-2,2-dimethyl-3-phenylpropane[13] (**11**) were synthesized by reaction of the corresponding tosylate with KI or LiCl in DMF. The tosylate (**12**) and the benzenesulfonate (**13**) were prepared by standard procedures. *p*-Toluensulfonylhydrazide was obtained from reaction of hydrazine hydrate (Carlo Erba) with *p*-toluensulfonyl chloride (Fluka) in THF.[14] 1-Iodo-2-methyl-2-phenylpropane[15] (**14b**) was obtained by reaction of the corresponding tosylate with KI in DMF. 1-Chloro-2-methyl-2-phenylpropane (**14a**, Aldrich) and *t*-BuOK (Fluka) were commercially available and used as received. DMSO (Carlo Erba) was distilled under vacuum and stored over molecular sieves (4A).

2,2-Dimethyl-3-phenylpropen-1-al.[16] 2,2-Dimethyl-3-phenylpropen-1-al was prepared by oxidation of 2,2-dimethyl-3-phenylpropan-1-ol (7.8 g, 47.5 mmol) with pyridinium chlorochromate (PCC)[17] (15.4 g, 71.5 mmol) in anhydrous CH_2Cl_2. The reaction mixture was kept at room temperature for 2 h. Diethyl ether was added, and the supernatant solution was decanted from the black gum. Evaporation of the solution produced crude aldehyde that was purified by distillation under vacuum.

Tosylhydrazone of 2,2-Dimethyl-3-phenylpropen-1-al (18). A solution of 2.7 g (14.5 mmol) of *p*-toluensulfonylhydrazine in 45 mL of ethanol and 2.2 mL of acetic acid was treated with 2.34 g (14.4 mmol) of the aldehyde dissolved in 2.9 mL of ethanol. The reaction mixture was kept at room temperature for 2 h and later cooled to 0 °C. Then ice-cooled water was added and the tosylhydrazone **18** precipitated after a while. The solid was filtered and recrystallized from ethanol/water (50:50): 1.645 g, 34% yield; mp 136−137 °C (lit.[10] mp 137 °C); ^{1}H NMR ($CDCl_3$) δ 1.0 (6H, s), 2.4 (3H, s), 2.6 (2H, s), 6.85−6.95 (2H, m), 7.0 (1H, s), 7.1−7.2 (3H, m), 7.2−7.8 (4H, dd); ^{13}C NMR ($CDCl_3$) δ 21.6, 24.9, 39.0, 46.9, 126.1, 127.8, 127.9, 129.4, 130.2, 135.1, 137.3, 143.9. MS (EI$^+$) 240 (49.6), 239 (61.8), 92 (44.2), 91 (100.0).

Decomposition of the Tosylhydrazone 18 with Sodium Methoxide. The tosylhydrazone of **18** (0.59 g, 1.8 mmol) was dissolved in 25 mL of diglime, sodium methoxide (0.49 g, 7.2 mmol) was added to this solution, and the flask was gradually heated in an oil bath. At 150 °C, decomposition of tosylhydrazone was observed, developing a yellow color. After 2 h, the reaction was quenched with addition of an excess of ammonium nitrate and 50 mL of water, and then the reaction mixture was extracted with diethyl ether. The mixture of the reaction was chromatographed over silica gel and eluted with petroleum ether. The less polar fraction was analyzed by GC−MS, giving a complex mixture of products with molecular weight of 146.

General Procedures for the Reaction of 1 with *t*-BuOK. The reaction was carried out in a 20 mL, three-necked Schlenk tube, equipped with nitrogen gas inlet, a condenser with a cooling jacket, and a magnetic stirrer. The tube was charged with nitrogen and then with 10 mL of dried DMSO and 1.2 mmol of *t*-BuOK, and the substrate was added. After varying determined times, the reaction was quenched with an excess of ammonium nitrate and 10 mL of water, and then the mixture was extracted with diethyl ether. The products were quantified by GC by the internal standard method, immediately after extraction.

1,1-Dimethyl-2-phenylcyclopropane (5).[10] Compound **5** was isolated from the reaction of **1** with *t*-BuOK by silica gel chromatography with petroleum ether and further purified by distillation: ^{1}H NMR ($CDCl_3$) δ 0.79 (3H, s), 0.66−0.91 (2H, m), 1.22 (3H, s), 1.84−1.91 (1H, m) 7.13−7.29 (5H, m); ^{13}C NMR ($CDCl_3$) δ18.4, 19.0, 20.3, 27.5, 29.8, 125.5, 127.8, 128.9, 140.3; MS (EI$^+$) 146 (31.1), 131 (100.0), 116 (17.6), 91 (34.3).

2,2-Dimethyl-3-phenylpropyl *t*-Butyl Ether (9). Compound **9** was isolated from the reaction of **1** with *t*-BuOK by silica gel chromatography with petroleum ether: ^{1}H NMR ($CDCl_3$) δ 0.8(6H, s), 1.2 (9H, s), 2.5 (2H,s), 2.9 (2H, s), 7.1−7.3 (5H, m); ^{13}C NMR ($CDCl_3$) δ 24.7, 27.6, 35.2, 44.9, 69.1, 72.0, 125.6, 127.5, 130.7, 139.5; MS (EI$^+$) 164 (1.77), 146 (6.72), 92 (14.70), 91 (70.97), 57 (100.00), 43 (4.60), 41 (27.80).

3,3-Dimethyl-4-phenylbutyl Methyl Sulfoxide (10). Compound **10** was isolated from the reaction of **1** with *t*-BuOK by silica gel chromatography with diethyl ether: ^{1}H NMR ($CDCl_3$) δ 1.0 (6H, s), 1.5−1.8 (2H, m), 2.60 (3H,s), 2.61 (2H, s), 2.7−2.9 (2H, m), 7.1−7.3 (5H, m); ^{13}C NMR ($CDCl_3$) δ 26.1, 26.2, 33.7, 33.8, 38.2, 48.1, 50.0, 125.9, 127.6, 130.2, 137.9; IR (KBr) cm^{-1} 1055.8; GC−MS analysis: this compound decomposes in the injector giving the product that has lost $CH_3S(O)H$ with MS (EI$^+$) 160 (5.2), 92 (38.0), 91 (81.8), 69 (100.0), 68 (12.4) and the peak of the giving compound with MS (EI$^+$) 208 (14.4), 117 (31.6), 116 (12.9), 91 (41.2), 61 (100.0).

2-Methyl-2-phenylpropyl *tert*-Butyl Ether (16).[18] Compound **16** was isolated from the reaction of **14b** with *t*-BuOK by silica gel chromatography with petroleum ether: ^{1}H NMR ($CDCl_3$) δ 1.1 (9H, s), 1.3 (6H, s), 3.3 (2H, s), 7.1−7.4 (5H, m); ^{13}C NMR ($CDCl_3$) δ 25.8, 27.4, 38.7, 71.2, 72.2, 125.6, 126.2, 127.8, 148.3; MS (EI+) 150 (1.4), 120 (8.5), 92 (17.4), 91 (57.1), 57 (72.3), 43 (92.1), 41 (100).

3-Methyl-3-phenylbutyl Methyl Sulfoxide (17). Compound **17** was isolated from the reaction of **14b** with *t*-BuOK, by silica gel chromatography with diethyl ether: ^{1}H NMR ($CDCl_3$) δ 1.4 (6H, s), 1.9−2.2 (2H, m), 2.3−2.5 (2H,m), 2.4 (3H, s), 7.1−7.3 (5H, m); ^{13}C NMR ($CDCl_3$) δ 29.1, 29.5, 36.8, 37.9, 38.9, 50.9, 126.1, 126.5, 128.5, 147.7; IR (KBr) cm^{-1} 1055.8. GC−MS analysis: this compound decomposes in the injector giving the product that has lost $CH_3S(O)H$ with MS (EI+) 146 (8.0), 131 (45.1), 91 (41.0), 39 (100), and the peak of the giving compound with MS (EI$^+$) 194 (9.1), 119 (51.7), 91 (74.0), 75 (74.8), 61 (40.9), 41 (100).

(12) Yuan, K.; Scott, W. J. *J. Org. Chem.* **1990**, *55*, 6188.
(13) Duca, J. S.; Gallego, M. H.; Pierini, A. B.; Rossi, R. A. *J. Org. Chem.*, **1999**, *64*, 2626.
(14) Friedman, L.; Litle, R. L.; Reichle, W. R. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 1055.
(15) Collman, J. P.; Brauman, J. I.; Madonik, A. M. *Organometallics* **1986**, *5*, 310.
(16) Stork, G.; Dowed, S. R. *J. Am. Chem. Soc.* **1963**, *85*, 2178.
(17) *Vogel's Textbook of Practical Organic Chemistry, 5th ed.*; Longman Scientific & Technical: Essex, 1989; p 426.
(18) Zimmerman, H. E.; Carpenter, C. W. *J. Org. Chem.* **1988**, *53*, 3298.

Acknowledgment. This work was supported in part by the Consejo de Investigaciones de la Provincia de Córdoba (CONICOR) and the Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Argentina. J.E.A. gratefully acknowledges receipt of a fellowship from the Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET).

Supporting Information Available: ^{1}H and ^{13}C NMR and mass spectra of compounds **5**, **9**, **10**, and **16**−**18**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO9905165

Additions and Corrections

Vol. 63, 1998

Martin G. Banwell, Bernard L. Flynn, and Scott G. Stewart Selective Cleavage of Isopropyl Aryl Ethers by Aluminium Trichloride

Page 9139. Professor C. Szántay (Technical University of Budapest) has previously reported three examples of the title reaction: Szántay, C. *Acta Chim. Hung.* **1957**, *12*, 83. We thank Professor Szántay for drawing our attention to his work.

JO994003+

10.1021/jo994003+
Published on Web 07/20/1999