Tetrahedron Vol. 49, No 2, pp. 381-386, 1993
Printed in Great Britain

0040-4020/93 $5.00+.00

ALKYL-C VERSUS PHENYL-C REACTIVITY IN UNSYMMETRICAL CYCLOPROPENONES. REACTION OF METHYLPHENYLCYCLOPROPENONE WITH PYRAZOLES.

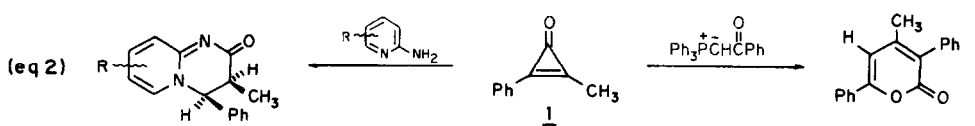
Albert Kascheres, Jair Correa Filho, and Sílvio Cunha*

Universidade Estadual de Campinas, Instituto de Química,
CP 6154, 13081 Campinas, SP, Brazil

(*Received in USA* 15 *October* 1992)

Abstract: Methylphenylcyclopropenone (1) reacts with pyrazole and 3,5-dimethylpyrazole to afford ketones (2) resulting from initial nucleophilic attack at methyl-C, in agreement with an AM1 calculation performed on 1. Intermediacy of dipolar species 3 accounts for products and allows incorporation of other nucleophiles (2-aminothiazole, 2-amino-4-methylpyridine, and o-phenylenediamine).

The fascinating chemistry of cyclopropenone derivatives has attracted the attention of numerous researchers over the past three decades,[1] with special emphasis on the behavior of diphenylcyclopropenone.[2] Unsymmetrical derivatives such as methylphenylcyclopropenone (1) have been found to react with nucleophiles at either of the two distinct conjugate positions. Thus, reaction of 1 with a triphenylphosphonium-enolbetaine afforded a 4-methyl-2-pyrone (eq.1),[3] while reaction with 2-aminopyridines produced 3-methyl-pyridopyrimidinones (eq.2).[4] In this work, HOMO-LUMO coefficients obtained from a theoretical treatment of 1 are used to gain insight into the question of alkyl-C versus phenyl-C reactivity.



1

The results of an AM1 calculation,[5] as implemented in the AMPAC package,[6] performed on geometrically optimized 1 are shown in Table 1. It may be seen that both HOMO and LUMO coefficients are largest at methyl-C.

Table 1. HOMO-LUMO Coefficients for 1

	1^{st} HOMO(p_z)	1^{st} LUMO(p_z)
Methyl-C	0.437	-0.500
Phenyl-C	0.297	0.438

Thus, it would appear that reaction of nucleophiles with 1 is kinetically favored at methyl-C. The reaction of 2-aminopyridines with 1 (eq.2) may actually proceed by way of an initial rapid and reversible reaction at methyl-C in conjunction with a slow and irreversible ketene-forming sequence involving attack at phenyl-C. This general idea is summarized in Scheme 1. Reaction of 1 with pyrazole, wherein hydrogen transfer in intermediates involves no loss of heterocycle aromaticity, shed new light on this question. An equimolar mixture of these reagents (ether, 3 days, room temperature) afforded ketone 2a (98%) together with unreacted 1 (50%). This result confirms the participation of a cyclopropanone intermediate resulting from initial nucleophilic attack at methyl-C. A second equivalent of pyrazole may be incorporated via dipolar species 3. The viability of interception of 3 by other nitrogen nucleophiles was studied. Thus, a mixture of 1 (one equivalent), pyrazole, and 2-aminothiazole[7] (two equivalents of each) produced 4a (80%) in addition to 2a (20%). The structure of 4a was suggested by the presence, in the ^{1}H NMR spectrum, of a high field benzylic-CH_2 AB pattern (δ2.08-2.58, J=13.5 Hz, cis relationship of CH_2 with respect to neighboring pyrazole nucleus), in addition to an OH absorption at δ3.13. Confirmation of the structure was provided by an X-ray analysis (fig.1). In a similar fashion, 2-amino-4-methylpyridine could be incorporated, resulting in formation of 5 (38%) and 2a (59%). The lower yield of 5 in relation to 4a may be attributed to greater steric crowding in intermediates involving the 2-aminopyridine nucleus. In fact, utilization of 3,5-dimethylpyrazole in the reaction of 2-amino-4-methylpyridine afforded only 2b (88%), while 4b (34%) and 2b (64%) were obtained from the reaction of 2-aminothiazole under these same conditions. A possible route to these products is presented in Scheme 1.

With the objective of comparing these results with those involving the possible participation of a ketene intermediate, the above reactions of pyrazole were repeated with diphenylcyclopropenone 6 in substitution of 1 (see Scheme 2). In the case of 2-aminothiazole, formation of the previously reported 7[7] (78%) was observed, in addition to 8[8] (20%, mixture of diastereomers). In the presence of 2-amino-4-methylpyridine, the previously reported 9[9] (a ketene rearrangement product, 83%) was produced, in addition to 8 (11%). These results reflect the inherent nucleophilic superiority of aminothiazoles and aminopyridines, which may only be brought to light in irreversible ketene-forming processes. The extensive incorporation of pyrazoles in the competition studies of 1 may be attributed to the formation of relatively stable cyclopropanone intermediates resulting from reaction at methyl-C. In some cases, the pyrazole nucleus in 3 may be removed in a later phase of the reaction, as

Scheme 1

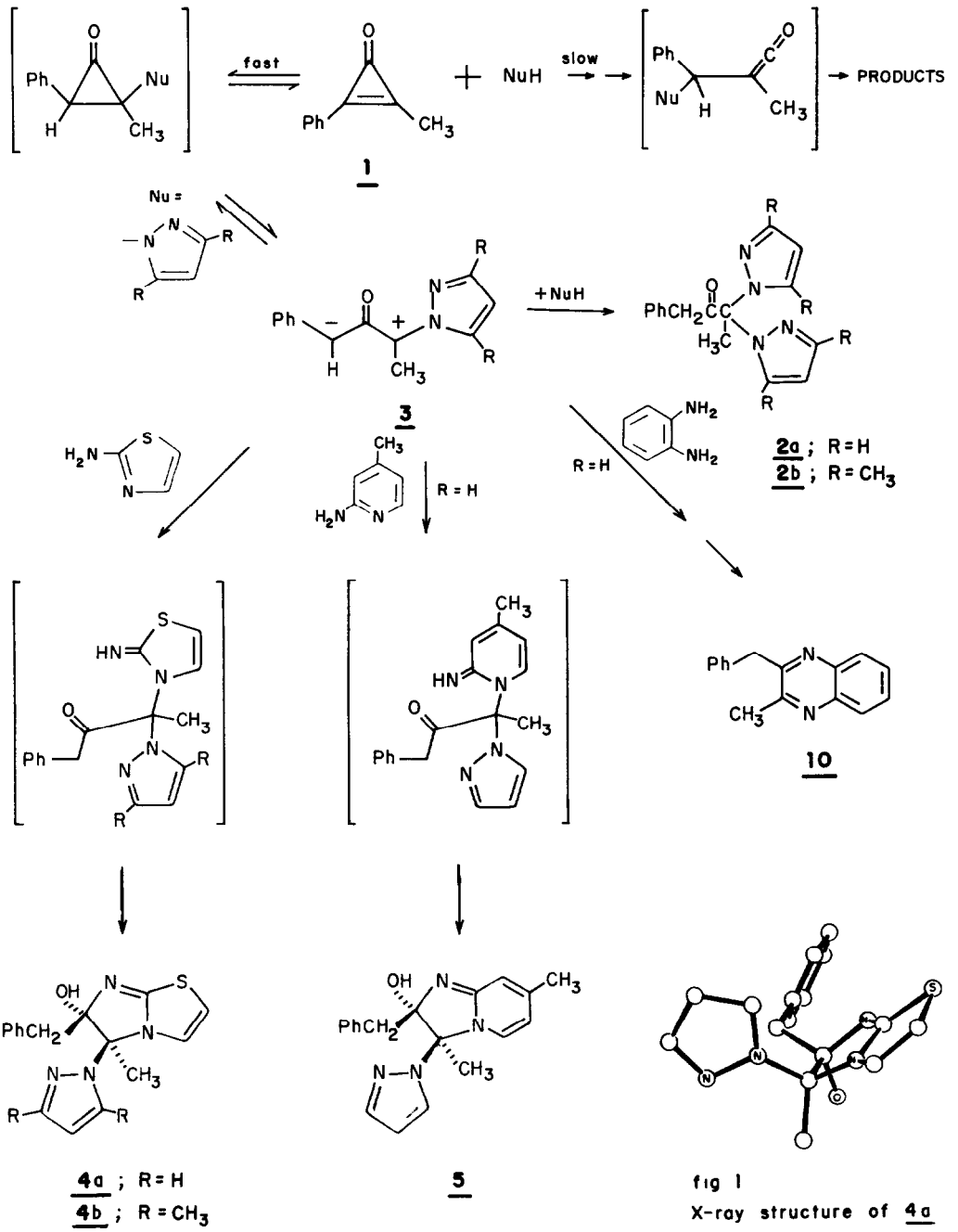
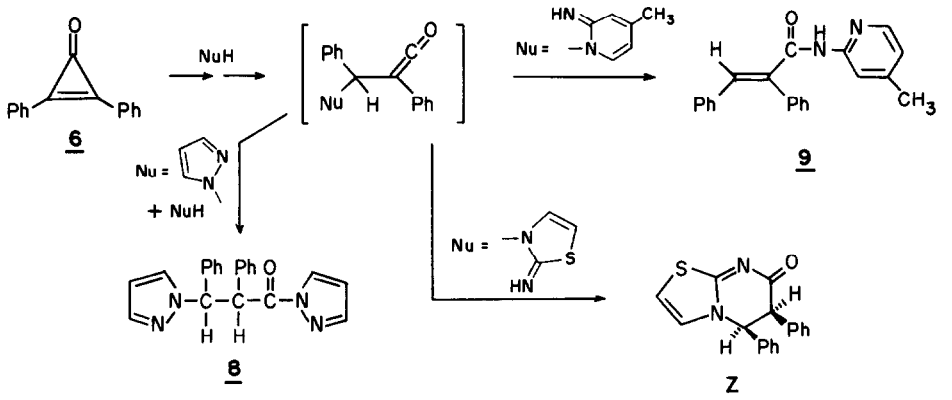


fig 1
X-ray structure of 4a

illustrated with o-phenylenediamine (which does not react with 1 in the absence of pyrazole), wherein quinoxaline 10 (80%) was formed.

Scheme 2



EXPERIMENTAL

The ^{1}H NMR spectra were recorded with a Bruker AW-80 or a Varian Gemini 300 MHz spectrometer using TMS as internal standard. Melting points were determined on a Hoover-Unimelt apparatus and are uncorrected. Elemental analyses were performed by Universidade Estadual de Campinas, Instituto de Química, Brazil.

Reaction of Methylphenylcyclopropenone (1) with Pyrazoles.

A solution containing 1 (1.00 mmol) and pyrazole or 3,5-dimethylpyrazole (2.00 mmol) in ether (3 mL) was allowed to stand at room temperature for 3 days. The reaction mixtures containing 2a-b were treated as follows:

2a (from 1 and pyrazole): Evaporation of the solvent afforded a yellow oil which was submitted to column chromatography (florisil, benzene as eluent) to yield a colorless oil (98%): IR (film) 1739 cm^{-1}; ^{1}H NMR (CCl_4) δ2.30 (3H,s), 3.60 (2H,s), 6.25 (2H,dd,J=2.7 and 1.8 Hz), 7.16 (5H,m), 7.30 (2H,d,J=2.7 Hz), 7.50 (2H,d,J=1.8 Hz). Anal. Calcd for $C_{16}H_{16}N_4O$: C,68.55; H,5.75; N,19.99. Found: C,68,89; H,5.84; N,20.17.

2b (from 1 and 3,5-dimethylpyrazole): The solution (after concentration of the mixture to one-half volume) was decanted from colorless crystals (98% yield): mp 149-150°C; IR(KBr) 1742 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ1.70(6H,s), 2.10(6H,s) 2.30(3H,s), 3.90(2H,s), 5.70(2H,s), 7.20(5H,m). Anal. Calcd for $C_{20}H_{24}N_4O$: C,71.39; H,7.20; N,16.66. Found: C,71.66; H,7.29; N,16.78.

Reactions of Methylphenylcyclopropenone (1) with Pyrazoles in the Presence of 2-Aminothiazole, 2,Amino-4-methylpyridine, or o-Phenylenediamine.

Reactions were performed as described above with the addition of aromatic amine (2.00 mmol). The reaction mixtures containing 4a-b,5, or 10 were treated as follows:

4a (from 1, pyrazole, and 2-aminothiazole): The solvent was decanted from colorless crystals (80% yield): mp 132-133°C; IR(KBr) 3226, 1581, 1548 cm^{-1}; ^1H NMR ($CDCl_3$) δ2.08(1H,d,J=13.5 Hz), 2.16(3H,s), 2.58 (1H,d,J=13.5 Hz), 3.13(1H,br), 5.96(1H,dd, J=4.8 Hz), 6.33(1H,dd,J=2.4 and 1.8 Hz), 6.46(1H,d,J=4.8 Hz), 7.25(6H,m), 7.60(1H,d,J=1.8 Hz). Anal. Calcd for $C_{16}H_{16}N_4OS$: C, 61.52; H, 5.16; N, 17.94. Found: C,61.66; H,4.92; N,17.83. Removal of solvent from the soluble fraction, followed by column chromatography of the residue (florisil, benzene as eluent), afforded 2a (20%) as a colorless oil.

4b (from 1,3,5-dimethylpyrazole, and 2-aminothiazole): Ether (3mL) was added to the reaction mixture, and the solvent was decanted from colorless crystals (34%): mp 134-135°C; IR(KBr) 3405, 1587, 1541 cm^{-1}; ^1H NMR ($CDCl_3$) δ2.16(3H,s), 2.21(6H,s), 2.25-2.45(2H,AB,J=12.0 Hz), 2.80 (1H,br), 5.87(1H,s), 5.97(1H,d, J=4.8 Hz), 6.59(1H,d,J=4.8 Hz),7.25(5H,m). Anal.Calcd for $C_{18}H_{20}N_4OS$: C,63.53; H,5.92; N,16.46. Found: C,63.38; H,5.78; N,16.42. Concentration of the soluble fraction to one-quarter volume afforded colorless crystals of 2b(64%).

5(from 1, pyrazole, and 2-amino-4-methylpyridine): The solvent was decanted from colorless crystals (38%): mp 150-151°C; IR(KBr) 3434, 1655, 1560 cm^{-1}; ^1H NMR ($CDCl_3$) δ2.04(3H,d, J=0.9 Hz), 2.07(1H,br), 2.09(3H,s), 2.16(1H,d,J=13.8 Hz), 2.58(1H, d, J=13.8 Hz), 5.59(1H,dd,J=7.0 and 1.8 Hz), 6.25(2H,m), 6.77(1H,d, J=7.0 Hz), 7.10(5H,m), 7.24(1H,d,J=2.7 Hz), 7.54(1H,d,J=1.5 Hz). Anal. Calcd for $C_{19}H_{20}N_4O$: C,71.22; H,6.30; N,17.48. Found: C,70.78; H,6.08; N,17.21. Removal of solvent from the soluble fraction, followed by column chromatography of the residue (florisil, benzene as eluent), afforded 2a(59%) as a colorless oil.

10 (from 1, pyrazole, and o-phenylenediamine, 1.0 mmol of each): Evaporation of the solvent afforded an orange oil which was submitted to column chromatography (florisil, 90% benzene-ether as eluent) to yield a pale-yellow solid (80%): mp 54-55°C; IR(KBr) 1595, 1560, 1478 cm^{-1}; ^1H NMR (CCl_4) δ2.50(3H,s), 4.24(2H,s), 7.13(5H,m), 7.52(2H,m), 7.88(2H,m). Anal. Calcd for $C_{16}H_{14}N_2$: C,82.05; H,5.98; N,11.97. Found: C,82.35; H,5.77; N,12.20.

Reactions of Diphenylcyclopropenone (6) with 2-Aminothiazole or 2-Amino-4-methylpyridine in the Presence of Pyrazole.

Reactions were performed as described above for 1. The reaction

mixtures containing 7 and 8 or 8 and 9 were treated as follows:

7 (from 6, pyrazole, and 2-aminothiazole): The solvent was decanted from colorless crystals (78%): mp 167-170°C (lit[7] mp 167-170°C). The residue obtained upon evaporation of the solvent was submitted to column chromatography (florisil, benzene as eluent) to afford 8 (20%) as a mixture (2:1) of diastereomers (A=major, B=minor): mp 166-172°C; IR(KBr) 1716, 1496, 1415 cm^{-1}; ^1H NMR ($CDCl_3$) δ5.93(1H,t,J=2.1 Hz,A), 6.03(1H,d, J=11.8 Hz,A), 6.06(1H,d,J=11.6 Hz,B), 6.20(1H,t,J=2.1 Hz,B), 6.31 (1H,dd,J=2.8 and 1.4 Hz,A), 6.34(1H,dd,J=2.8 and 1.4 Hz B), 6.36(1H,d,J=11.6 Hz,B), 6.51(1H,d,J=11.8Hz,A), 7.09-7.58 (m,phenyls,A and B), 7.65-7.71 (m,pyrazole H_3 and H_5, A and B), 8.02(1H,d,J=2.8Hz,A), 8.11(1H,d,J=2.8Hz,B). Anal. Calcd for $C_{21}H_{18}N_4O$: C,73.67; N,5.30; H,16.36. Found: C,74.07; H,5.19; N,16.08.

9 (from 6, pyrazole, and 2-amino-4-methylpyridine): Evaporation of the solvent afforded an oil which was crystallized from methylene chloride-petroleum ether (30-60°C) to produce a colorless solid (83%): mp 131-132°C (lit[9] mp 131-132°C). The mother liquor yielded 8 (11%, isolated as described above).

ACKNOWLEDGEMENT. The authors thank Dr. Julio Zukerman-Schpector of the Instituto de Física e Química de São Carlos, DFQ, USP, CP 369, CEP 13560, São Carlos, SP, Brasil for the X-ray analysis.

REFERENCES AND NOTES

1. For the reviews on the reactivity of cyclopropenes (including cyclopropenones), see: (a) Potts, K.T.; Baum, J.S. Chem. Rev. 1974, 74, 189. (b) Eicher, T.; Weber, J. Top. Curr. Chem. 1975, 57, 1.(C) Deem, M.L. Synthesis 1982, 701.
2. Musicki; B. J. Org. Chem. 1991, 56, 110.
3. Eicher, T.; von Angerer, E.; Hansen, A.M. Liebigs Ann. Chem. 1971, 746, 102.
4. Kascheres, A.; Kascheres, C.; Rodrigues, J.; Santana, A. J. Org. Chem., 1976, 41, 3546.
5. Good results have been obtained for small-ring systems using this method: Dewar, M.J.S.; Zoebisch, E.G.; Healy, E.F.; Stewart, J.J.P. J. Am. Chem. Soc., 1985, 107, 3902.
6. Dewar, M.J.S., Research Group, QCPE Bull., 1986, Program No.506.
7. This system did not react with 1 under the conditions employed here, in contrast to the reported behavior toward diphenylcyclopropenone: Kascheres, A.; Reyes, J.L.; Fonseca, S.M. Heterocycles, 1984, 22, 2529.
8. N-(α-phenylcinnamoyl)pyrazole (prepared from α-phenylcinnamoyl chloride and pyrazole) did not react with pyrazole under these conditions, thus ruling out a carbonyl addition pathway for the formation of 8.
9. Kascheres, A.; Rodrigues, J. J. Org. Chem., 1975, 40, 1440.