1,5 *vs.* 1,6 Intramolecular Homolytic Aromatic Substitution by Vinyl Radicals

Attilio Citterio,*[a] Roberto Sebastiano,[a] Antonietta Maronati[a] Roberto Santi*[b] and Fabrizio Bergamini[b]

[a] *Politecnico di Milano, Dipartimento di Chimica, Via Mancinelli 7, 20131-Milano Italy*
[b] *Istituto Donegani S.p.A., Via Fauser 4, 28100-Novara, Italy*

Manganese(III) acetate oxidation of substituted diethyl benzylmalonates in the presence of alkynes affords tetrahydronaphthalene derivatives **3, 6, 7** and spiro[4,5]decatriene derivatives **4** or **5**, through competitive 1,5 and 1,6 intramolecular aromatic substitution by vinyl radicals.

A tandem sequence of carbon free-radical addition–cyclization reactions is a straightforward and useful annulation methodology for the synthesis of polysubstituted cyclopentane and cyclohexane rings.[1,2] When the addition involves an aromatic nucleus 6-*endo*-cyclization is preferentially observed.[3] However, examples of aromatic *ipso* substitution (intermolecular by acyl and alkyl radicals[4] and 1,5-intramolecular by alkyl,[5] aryl[6,7] and vinyl[8,9] radicals) are known, but few examples of the formation of spirocyclohexadiene derivatives have been reported.[6] We report herein evidence for the importance of the 5-*exo-dig*-cyclization in the intramolecular addition of vinyl radical to arenes by isolation of spirocyclohexadiene derivatives, products of rearrangement or side-chain hydrogen elimination, depending on the substituents on the aromatic unit.

The reaction investigated was the radical addition–cyclization of substituted diethyl benzylmalonates **1** and alkynes **2** induced by manganese(III) acetate, recently reported by us to afford mainly dihydronaphthalene derivatives **3**[10] (Scheme 1).

As indicated in Table 1,† the product distribution of these reactions is strongly dependent on the substituents of the aromatic ring. Dihydronaphthalene derivatives **3** are in fact efficiently formed with the parent, 4-isopropyl and 3-methyl derivatives (**1f**, **1h** and **1i**), but are side products with substrates **1a**, **1b**, **1e** and **1g** having electron-releasing *para* or *ortho* substituents. Moreover, a mixture of dihydronaphthalene isomers **3**, **4** and **5** is observed in reactions with derivatives **1c** and **1d**, which possess electron-withdrawing groups in the *para*-position.

Spiro[4,5]deca-1,6,9-trien-8-one derivatives **6** are the main products in reactions with 4-F (**1b**) and 4-OMe (**1a**) derivatives with all the alkynes used, whereas with 4-CF_3 (**1c**) and 4-CO_2Me (**1d**) derivatives the 3,3-diethoxycarbonylspiro[4,5]deca-1,6,9-triene derivatives **7** ($R^1 = CF_3$ or CO_2Me, $R^2 = H$, $R^4 = H$, $R^5 = OAc$) were isolated in significant amounts.

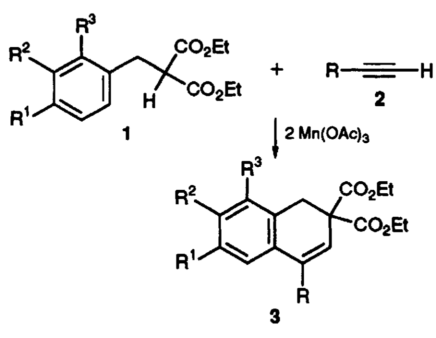
Moreover, spiro[4,5]deca-1,7,9-trien-6-one **7** ($R^1 = R^2 = H$, R^4, $R^5 = O$) was the major product in the reaction of diethyl 2-fluorobenzylmalonate **1e** with oct-1-yne or prop-2-ynyl alcohol. The 4-methyl derivative **1g** behaves peculiarly giving, along with product **3**, the unexpected compound **8**, which includes two malonate units per alkyne unit.

These data clearly indicate that spyrocyclohexadienyl radicals **13** are crucial in the intramolecular homolytic aromatic substitution by vinyl radicals **11** and suggest a

Table 1 Product distribution in the addition–cyclization reactions of diethyl benzylmalonates **1** with alkynes **2** induced by $Mn(OAc)_3$

		Product yield (%)			
1	**2**	**3**	**6**	**7**	**8**
1a	**2a**	10	79	—	—
1a	**2b**	13[a]	48[b]	—	—
1b	**2a**	28	66	—	—
1b	**2c**	32	62	—	—
1b	**2d**	13	69	—	—
1c	**2a**	65[c]	—	12[d]	—
1c	**2c**	41[e]	—	6[d]	—
1c	**2d**	63[f]	—	18[d]	—
1d	**2d**	60[g]	—	31[d]	—
1e	**2a**	6	—	77[h]	—
1e	**2b**	12	—	65[h]	—
1f	**2d**	92	—	—	—
1g	**2a**	41	—	—	55
1g	**2c**	37	—	—	52
1g	**2d**	23	—	—	67
1h	**2d**	85	—	—	—
1i	**2a**	82	—	5[d]	—

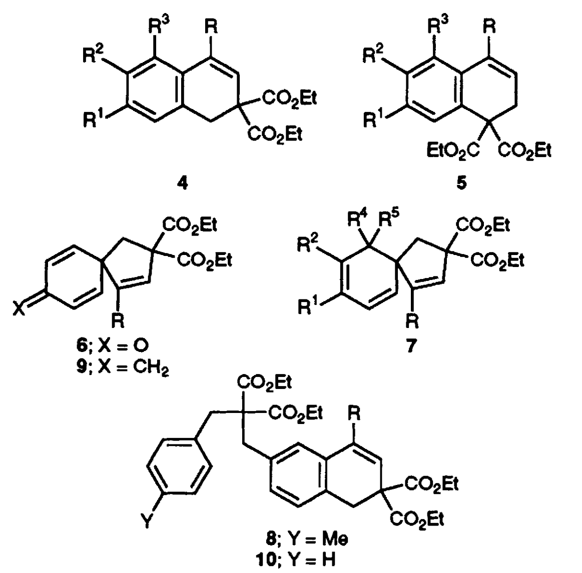
[a] Mixture of **3** ($R = CH_2OH$, 46%) and **3** ($R = CH_2OAc$, 54%). [b] Mixture of **6** ($R = CH_2OH$, $R^4,R^5 = O$, 63%) and **6** ($R = CH_2OAc$) (37%). [c] Isomers **4** and **5** ($R = n\text{-}C_6H_{13}$) were also isolated in 20 and 3% yield. [d] Compound **7** ($R^3,R^4 = H$, $R^5 = OAc$). [e] Isomers **4** and **5** ($R = SiMe_3$) were also isolated in 38 and 11% yield. [f] Isomers **4** and **5** (R = Ph) were also isolated in 16 and 4% yield. [g] Isomers **4** and **5** (R = Ph) were also isolated in 3 and 1% yield. [h] Compound **7** ($R^4,R^5 = O$).



1a, $R^1 = OMe$, $R^2 = R^3 = H$
1b, $R^1 = F$, $R^2 = R^3 = H$
1c, $R^1 = CF_3$, $R^2 = R^3 = H$
1d, $R^1 = CO_2Me$, $R^2 = R^3 = H$
1e, $R^1 = R^2 = H$, $R^3 = F$
1f, $R^1 = R^2 = R^3 = H$
1g, $R^1 = Me$, $R^2 = R^3 = H$
1h, $R^1 = Pr^i$, $R^2 = R^3 = H$
1i, $R^1 = R^3 = H$, $R^2 = Me$

2a, $R = n\text{-}C_6H_{13}$
2b, $R = CH_2OH$
2c, $R = SiMe_3$
2d R = Ph

Scheme 1

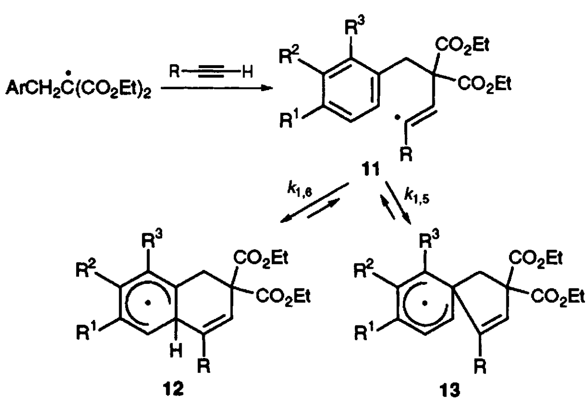


preference for the 5-*exo-dig*- over the 6-*endo-dig*-cyclization mode ($k_{1,5}/k_{1,6}$ = 6–7) (Scheme 2).

The formation of dihydronaphthalenes **3** appears to depend more on the selective rearrangement of the cyclohexadienyl cation arising from the oxidation of **13** than on a true 6-*endo-dig* radical cyclization through **12**. Moreover, the formation of isomers **4** and **5** of **3** is indicative of a fragmentation of the weaker sp^3–sp^3 C–C bond of intermediate **13** to give the corresponding primary radical which partitions between homolytic aromatic substitution or addition to the styrenic double bond followed by fragmentation of the resulting cyclopropylmethyl radical and homolytic aromatic substitution by the resulting 3-arylprop-2-enylmalonyl radical. This last step has recently been independently proved by us.[11]

The wide range of pathways open to intermediate **13** is further shown by the formation of compound **8** in the reaction with the 4-methyl derivative **1g**. We suggest that the intermediate spirocyclohexadienyl radical **13** in this case is oxidized with proton loss from the pendent methyl group affording a methylenecyclohexadiene spiro derivative **9** and that this efficiently traps malonyl radicals affording, after oxidation and cationic 1,2-alkenyl shift, the diadduct **8**. The good yield of unrearranged **3** observed in reactions with the 4-isopropyl derivative **1h** supports further the key role of the deprotonation by a base of the cyclohexadienyl cation formed by oxidation of the *para*-methyl substituted radical **13**. To prove this hypothesis, compound **9** (R = n-C_6H_{13}) was independently synthesized and found to be slowly converted by acetic acid at 60 °C to the corresponding tetrahydronaphthalene **3**, but, when introduced in the reaction of **1f** and **2a** with $Mn(OAc)_3$, it is converted to compound **10**, analogous to diadduct **8**.

These results clearly indicate that 1,5-regioselectivity in the intramolecular addition of γ-arylalkyl radicals to aromatic compounds is as important as in the olefin series[12] but that a complex interplay of factors (reversibility of the addition to π-system, influence of aromatic substituents on the oxidizability of cyclohexadienyl radical intermediates, radical and ionic rearrangements of cyclohexadienyl intermediates) can mask its involvement. A more careful control of substrates and reaction conditions (from radical sources, to substituent effect on radical and cation intermediates, to redox properties of the medium, *etc.*) would provide new access to spirocyclic derivatives and widen the synthetic potential of the intramolecular homolytic aromatic substitution.



Scheme 2

The work was supported by the Commission of European Communities (Contract ERBSCI*CT910750), and Murst (Rome).

Received, 8th December 1993; Com. 3/07278I

Footnote

† Reported yields of cyclization products were determined from the reaction mixture by GLC using internal standards. All products were isolated by column chromatography and fully characterized by ^1H NMR, ^{13}C NMR, mass and IR spectroscopy. ^1H NOE experiments were carried out in order to ascertain the structure of compounds **3**, **4**, **5**, **7** and **8**.

References

1 C. P. Jasperse, D. P. Curran and T. L. Fevig, *Chem. Rev.*, 1991, **91**, 1237; D. P. Curran, *Synthesis*, 1988, 417; M. Ramaiah, *Tetrahedron*, 1987, **43**, 3541; D. Hart, *Science*, 1984, **223**, 883.

2 C. Thebtaranonth and Y. Thebtaranonth, *Tetrahedron*, 1990, **46**, 1412; E. R. Laird and W. I. Jorgenson, *J. Org. Chem.*, 1990, **55**, 9; S. A. Hitchcock and G. Pattenden, *Tetrahedron Lett.*, 1992, 4843.

3 A. L. J. Beckwith and K. U. Ingold, in *Rearrangements in Ground and Excited States*, ed. P. de Mayo, Academic, New York, 1980, vol. 1, pp. 188–200; A. L. J. Beckwith, *Rev. Chem. Intermediates*, 1986, **7**, 143.

4 T. Caronna, A. Citterio and M. Bellatti, *J. Chem. Soc., Chem. Commun.*, 1976, 987; M. Tiecco, *Acc. Chem. Res.*, 1980, **13**, 51.

5 J. J. Kohler and W. N. Speckamp, *Tetrahedron Lett.*, 1977, 631.

6 M. Sainsbury, *Tetrahedron*, 1980, **36**, 3327.

7 W. B. Motherwell and A. M. K. Pennell, *J. Chem. Soc., Chem. Commun.*, 1991, 877.

8 R. Leardini, D. Nanni, G. Pedulli, A. Tundo and G. Zanardi, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1591.

9 W. B. Motherwell, A. M. K. Pennell and F. Ujjainwalla, *J. Chem. Soc., Chem. Commun.*, 1992, 1067.

10 R. Santi, F. Bergamini, A. Citterio, R. Sebastiano and M. Nicolini, *J. Org. Chem.*, 1992, **57**, 4250. For similar 1,6-homolytic aromatic substitution processes see: A. Citterio and R. Santi, in *Free Radical in Synthesis and Biology*, ed. Minisci NATO ASI Serie C 260, Kluwer, Academic Press, Dordrecht, 1989, p. 187; A. Citterio, D. Fancelli, C. Finzi, L. Pesce and R. Santi, *J. Org. Chem.*, 1989, **54**, 2713; A. Citterio, R. Sebastiano, R. Santi and L. Pesce, *Synthesis*, 1990, 142; A. Citterio, R. Sebastiano, L. Pesce and R. Santi, *Synthesis*, 1990, 142; A. Citterio and R. Santi, *J. Org. Chem.*, 1989, **54**, 2703; A. Citterio, R. Sebastiano, A. Marion and R. Santi, *J. Org. Chem.*, 1991, **56**, 5328; A. Citterio, S. Cardani, R. Sebastiano and M. Nicolini, *Gazz. Chim. Ital.*, 1993, **123**, 1035.

11 A. Citterio, R. Sebastiano and M. Nicolini, *Tetrahedron*, 1993, **49**, 7743.

12 D. C. Spellmeyer and K. N. Houk, *J. Am. Chem. Soc.*, 1982, **104** 7162; A. L. J. Beckwith and C. H. Schiesser, *Tetrahedron*, 1985, **41**, 3925; D. C. Spellmeyer and K. N. Houk, *J. Org. Chem.*, 1987, **52**, 959.