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Radical Additions of Simple Piperazine-2,5-diones

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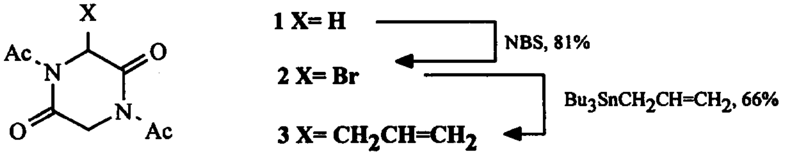
Abstract: The polar character of a simple piperazine-2,5-dione was investigated under intermolecular radical addition conditions. The results indicate that captodative radical of this kind neither show extreme nucleophilic nor electrophilic tendencies.

The formation of new carbon-carbon bonds employing small molecules as building blocks is crucial in organic synthesis and free radical chemistry has provided viable methods for such carbon-carbon chain extensions.[2-6] The intermolecular addition of radicals to alkenes remains an important and versatile procedure even though problems can be associated with radical reactivity and selectivity.[3,4] Alkyl radicals are generally accepted to be nucleophilic in nature and their rates of addition to electron-deficient alkenes are enhanced. As captodative radicals are substituted with both electron-donating and electron-withdrawing substituents,[7,8] a study of the "polar" character[3,4,9] of such radicals is pertinent to the design of syntheses involving such species. We now report addition reactions to olefins that employ a captodative radical.

The use of *n*-tributylallyltin in radical synthesis is well documented[10] and provides a method of allylation. When a solution of **2**, [11,12] prepared from 1,4-diacetylpiperazine-2,5-dione **(1)** [13] and NBS (1 equiv.), was treated with tributylallyltin in refluxing benzene, the 3-allyl derivative **(3)** was obtained as a colourless oil (66%).[14] Structure **3** was deduced from ^1H n.m.r. spectroscopy. The expected absence of the C*H*Br singlet at δ 6.87 in **(2)** was coupled with the appearance of a triplet (*J* 6.95 Hz) centred at δ 5.29 attributed to the methine hydrogen coupled to the two adjacent allyl protons (^1H-^1H COSY experiments). The resonances observed for the ring methylene shift upfield to δ 5.02, 5.15 and δ 4.07, 4.13 (*J* 18.87 Hz, AB system) from δ 5.21, 5.27 and δ 4.27, 4.34 (*J* 18.92, AB system) respectively compared to the monobromide.

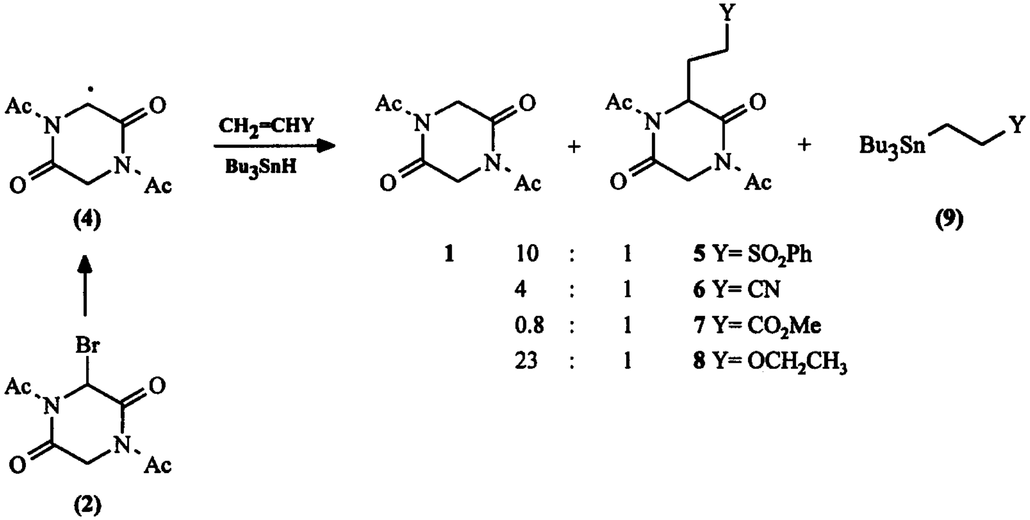


More importantly, competitive intermolecular additions of radical **4** derived from **2** to a variety of other alkenes were investigated. The reaction conditions were optimised for the addition to methyl acrylate. Thus the concentration of the alkene, modes of initiation and choice of reducing agents were all varied. The

conditions thus established[15] were kept constant while the alkene substituents were varied. The ratio of the directly reduced adduct to piperazinedione addition adduct obtained are depicted in Scheme 1.
The ratio of addition [adducts (5-8)] to reduction [product (1)] were determined by accurate ^{1}H n.m.r. integrations of the relevant spectra since adducts (5-8) have a characteristic triplet in the range 5.1-5.3 ppm attributed to the CH_2Y hydrogens.[16]

The proportion of radical addition to the alkenes at opposite ends of the polarity spectrum is low. Thus for example, electron deficient phenyl vinyl sulfone and the electron rich ethyl vinyl ether, show a marked preference for reduction to 1. In comparison, cyanoethene has moderate competition with reduction while methyl propenoate is captured preferentially to reduction. However, yields of the isolated addition adducts were disappointingly low. Alkene polymerisation and tributyltin radical capture of the alkene *c.f.* 9 were formed from the intermolecular addition. It has been reported[17] that captodative radicals are not efficient in chain propagation; short chains result and low yields may be accounted for.

Scheme 1.



(4)

(2)

(9)

1	10	:	1	**5** Y= SO$_2$Ph
	4	:	1	**6** Y= CN
	0.8	:	1	**7** Y= CO$_2$Me
	23	:	1	**8** Y= OCH$_2$CH$_3$

Despite the limitations the present study demonstrates the behaviour of the captodative radical in the addition to an alkene. Two competing reactions occur: The direct quenching of 4 by tributyltin hydride and the addition of 4 to alkene resulting in the formation of an intermediate addition adduct radical, which is then quenched by tributyltin hydride. Studies have shown that the rates of quenching of alkyl radicals with tributyltin hydride are relatively insensitive to substituents effects on the radical.[18,19] Thus assuming that the intermediate addition adduct radicals are reduced by tributyltin hydride at similar rates, the results suggest that the captodative radical 4 displays neither extreme nucleophilic nor electrophilic tendencies. This is because nucleophilic radicals favour addition to electron deficient alkenes and vice versa. The combined results from these studies show that the polar character of alkene have a major influence on the outcome of the reactions. These considerations are important if the use of radical reactions in the synthesis of more complicated piperazine-2,5-dione-containing structures is to be carried out efficiently. Conceivably, any such structure desired could be synthesized in this way by "tailormaking" an alkene to suit the polar nature of the radical generated from a suitable piperazine-2,5-dione precursor or vice versa.

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Reference and notes:

1. Joint appointee of Industrial Research Limited, Gracefield and Victoria University, Wellington.
2. For a comprehensive review see Curran, D.P. *Chem Rev.* **1991**, *91*, 1441.
3. Giese, B. *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 753.
4. Giese, B. *Radicals in Organic Synthesis - Forming New C-C Bonds*; Pergamon Press: Oxford. 1986.
5. Neumann, W.P. *Synthesis* **1987**, 665.
6. Giese, B. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 969.
7. Viehe, H.G. *Acc. Chem. Res.* **1985**, *18*, 148.
8. For a current review on the Captodative Effect see Sustmann, R.; Korth, H.G. *Adv. Phys. Org. Chem.* **1990**, *26*, 131.
9. Giese, B.; Mehl, W. *Tetrahedron Lett.* **1991**, *32*, 4275.
10. Keck, G.E.; Enholm, E.J.; Yates, J.B.; Wiley, M.R. *Tetrahedron* **1985**, *41*, 4079.
11. New compounds gave satisfactory spectral, analytical and/or high resolution mass spectral data in accordance with the assigned structures.
12. **2**: ^{1}H NMR δ 2.61 (s, 3H), 2.62 (s, 3H), 4.27, 4.37 (d, *J* 18.92 Hz, 1H), 5.21, 5.27 (d, *J* 18.92 Hz, 1H), 6.87 (s, 1H). The bromo derivative is unstable to prolonged storage and was characterised as 1,4-diacetyl-3-(*p*-chlorothiophenyl)piperazine-2,5-dione. m.p. 85-87 °C. ^{1}H NMR δ 2.55 (s, 3H), 2.56 (s, 3H), 3.98, 4.21 (d, *J* 18.3 Hz, 1H), 5.01, 5.24 (d, *J* 18.3 Hz, 1H), 6.22 (s, 1H), 7.4-7.6 (m, 4H). Found: C= 49.25, H= 3.79, N= 8.06, S= 9.53.
13. Franchimont, A.; Friedmann, H. *Recl. Trav. Chim. Pays-Bas* **1908**, *27*, 192.
14. **3**: ^{1}H NMR δ 2.57 (s, 3H), 2.59 (s, 3H), 2.63 (m, 2H), 4.07, 4.13 (d, *J* 18.87 Hz, 1H), 5.02, 5.15 (d, *J* 18.87 Hz, 1H), 5.18 (m, 2H), 5.29 (t, *J* 6.95 Hz, 1H), 5.75 (m, 1H). Found: C= 55.16, H= 5.78, N= 11.59.
15. A solution of **2** (1 molar equivalent, 0.4 M) in dry benzene and 2.5 molar equivalents of alkene was degassed. The reaction mixture was irradiated with UV light at room temperature while a solution of tributyltin hydride (1.1 molar equivalent, 0.3 M) and AIBN was added by the infinite dilution method

with a syringe pump at the rate of 0.05 mL/minute.

16. **5**: ^{1}H NMR δ 2.27 (m, 2H), 2.53 (masked m, 2H), 2.52 (s, 3H), 2.53 (s, 3H), 4.07, 4.13 (d, *J* 18.65 Hz, 1H), 5.05, 5.11 (d, *J* 18.65 Hz, 1H), 5.13 (t, *J* 7.8 Hz, 1H), 7.57 (m, 3H, aromatic), 7.85 (m, 2H, aromatic). **6**: ^{1}H NMR δ 2.17 (m, 2H), 2.57 (masked m, 2H), 2.57 (s, 3H), 2.58 (s, 3H), 4.05, 4.11 (d, *J* 18.69 Hz, 1H), 5.11, 5.18 (d, *J* 18.69 Hz, 1H), 5.20 (t, *J* 7.7 Hz, 1H). **7**: ^{1}H NMR δ 2.21 (m, 2H), 2.53 (masked m, 2H), 2.55 (s, 3H), 2.56 (s, 3H), 3.67 (s, 3H), 4.14, 4.20 (d, *J* 18.60 Hz, 1H), 5.13, 5.18 (d, *J* 18.60 Hz, 1H), 5.16 (t, *J* 8.27 Hz, 1H). **8**: ^{1}H NMR δ 1.10 (t, *J* 7.0 Hz, 3H), 2.10 (m, 1H), 2.29 (m, 1H), 2.56 (s, 3H), 2.57 (s, 3H), 3.36 (m, 2H), 3.48 (t, *J* 6.0 Hz, 2H), 4.10, 4.16 (d, *J* 18.67 Hz, 1H), 4.98, 5.04 (d, *J* 18.67 Hz, 1H), 5.28 (t, *J* 6.60 Hz, 1H).
17. Crich, D; Davies, J.W. *Tetrahedron* **1989**, *45*, 5641.
18. Ingold, K.U., Lusztyk, J., Scaiano, J.C. *J. Am. Chem. Soc.* **1984**, *106*, 343.
19. Johnston, L.J., Lusztyk, J., Wayner, D.D.M., Abeywickreyma, A.N., Beckwith, A.L.J., Scaiano, J.C., Ingold, K.U. *J. Am. Chem. Soc.* **1985**, *107*, 4594.

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