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Mechanistic Studies of Atom Transfer Addition Reactions of Iodomalononitriles to Alkenes. 1,2-Asymmetric Induction in an Iodine Atom Transfer Reaction.

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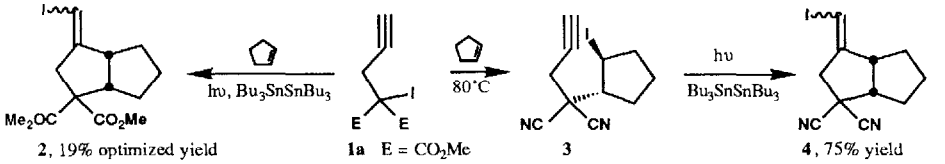
Summary: An unusual stereoselective iodine transfer to a benzylic radical helps to show that atom transfer additions of iodomalononitriles to alkenes occur by a radical mechanism.

We have recently introduced propargyl- and allyliodomalonotriles as new reagents for atom transfer annulation reactions.[2] These second generation reagents followed directly from our previous work on propargyl- and allyliodomalonic esters.[3] Despite the structural similarities, these two classes of reagents exhibited strikingly different behavior. The representative example shown in eq 1 illustrates these differences: 1) iodomalonic esters **1a** did not add to 1,2-di- and trisubstituted alkenes in useful yields but iodomalononitriles **1b** did, 2) yields with iodomalonic esters were improved by using catalytic quantities of a distannane, but yields from iodomalononitriles were reduced, 3) irradiation of the iodomalonic ester reactions with a sunlamp increased both the conversion rate and the yield but irradiation of the iodomalononitrile reactions increased only the conversion rate—the yield actually decreased, 4) annulation reactions of iodomalonates usually (but not always) progressed directly to the (iodomethylene)-cyclopentanes **2**, but the annulations of iodomalononitriles almost always stopped at the adduct stage. The adducts **3** could subsequently be isomerized to the vinyl iodides **4**.

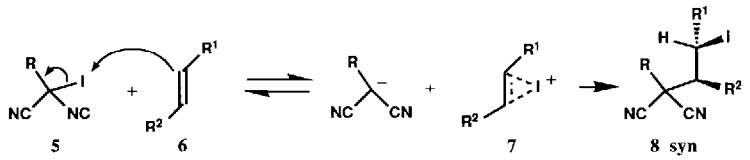
The above observations seemed to provide circumstantial evidence that the reactions of iodomalononitriles proceed through an ionic mechanism involving iodonium ions. However, other circumstantial evidence appeared more consistent with a radical mechanism.[4] For example, we could retard the reactions by adding a radical trap like TEMPO (although we could never isolate any of the expected radical coupling products), and we could not promote the reactions by adding reagents that might aid in formation of the iodonium ion. More compellingly, the regiochemistry with substituted styrenes gave products consistent with the radical path and not the ionic path. A more discerning series of experiments has now shown that additions of iodomalononitriles to alkenes do not proceed by an ionic mechanism but instead follow a standard radical mechanism. Included in this evidence is the observation of a stereoselective iodine transfer reaction, the results of which nicely fit an emerging model for 1,2-asymmetric induction in radical reactions.[5]



2, 19% optimized yield — **1a** E = CO_2Me; **1b** E = CN — **3** — **4**, 75% yield

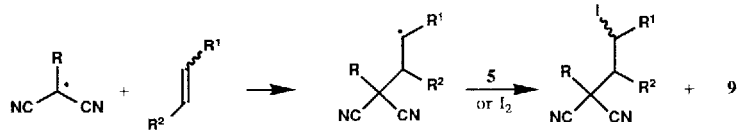
eq 1

We envisioned that the ionic mechanism shown in eq 2 was a potential alternative to the standard atom transfer mechanism shown in eq 3.[6] The ionic mechanism invokes the intermediacy of an iodonium ion **7**, which could either be formed from molecular iodine (the color of which is easily visible during the reactions), or from the iodomalononitrile itself (as eq 2 shows). Iodomalononitriles should be good sources of positive iodine, and we have already observed ionic reactions of iodoacetoacetates.[7]



eq 2

5 6 7 8 syn

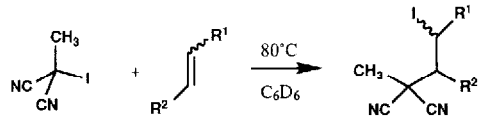


eq 3

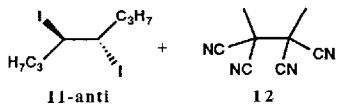
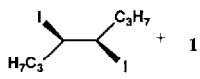
9 6 10 8 syn + anti

The key difference that distinguishes these two mechanistic paths is stereochemistry. The iodonium mechanism predicts a stereospecific addition reaction, but the radical mechanism does not. In preparative experiments, adducts were generally isolated as mixtures of stereoisomers, but control experiments quickly showed that these adducts were not always stable to the reaction conditions.[4] To learn about the kinetic stereochemical outcome, we conducted several reactions under the standard conditions (80 °C, 0.1M) in C_6D_6 and followed the reactions by ^1H NMR. The results with two pairs of alkenes, *E*- and *Z*-1-phenyl-1-propene (**6a**/*E* and *Z*) and *E*- and *Z*-4-octene (**6b**/*E* and *Z*) are summarized in Table 1. These two pairs exhibit very different behavior.

Table 1. Additions of Methyliodomalononitrile to *E*/*Z* Alkenes



5, R = CH_3 **6a**/*E* trans R^1 = Ph, R^2 = CH_3 **8a,b** syn/anti
6a/*Z* cis R^1 = Ph, R^2 = CH_3
6b/*E* trans R^1 = R^2 = C_3H_7
6b/*Z* cis R^1 = R^2 = C_3H_7

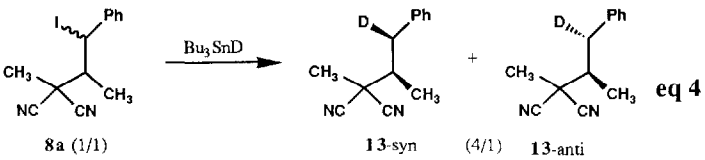
Entry	Alkene	Reaction Time	% Conv.	Ratio **8a** or **8b** syn/anti (yield)	Other Products
1	**6a**/*E*	30 min	50%	6/1	None
		90 min	>90%	1.1/1 (90%)	
2	**6a**/*Z*	30 min	40%	6/1	None
		90 min	>90%	1.1/1 (85%)	
3	**6b**/*E*	20 min	40%	1.1/1	
		90 min	>90%	1/1.1 (15%)	**11**-anti **12**
4	**6b**/*Z*	20 min	30%	1.1/1	
		90 min	>90%	1/1.1 (10%)	**12**
					11-syn

The styrene derivatives **6a** (entries 1, 2) were more reactive than the octenes **6b** (entries 3, 4), and gave much higher yields of adducts. Within each pair, the *E*-isomer was marginally more reactive than the *Z*-

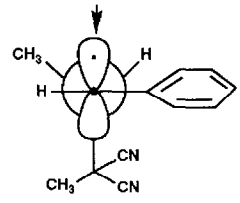
isomer. In the case of the octenes, no *E*/*Z* isomerization could be detected.[8] In contrast, small amounts of *E*-1-phenyl-1-propene (**6a**/*E*) were observed in the reaction of the *Z* isomer **6a**/*Z*. However, given the small rate differences between the *E* and *Z* isomers, we conclude that very little of the product in the reaction of the *Z*-isomer resulted from addition to the isomerized *E* alkene. In the case of the octene additions, significant amounts of vicinal diidodides (**11**-syn or anti) were formed. Unlike the adducts from the iodomalononitrile, these diiodides were formed stereospecifically. The diiodides probably form through the intermediacy of molecular iodine, and the stereospecific addition of I_2 to alkenes is a known reaction that is readily reversible.[9] Also observed in the reactions with the octenes was the coupled malononitrile **12**. The formation of these dimers (I_2 and **12**) is almost certainly the result of the slow rate of addition of the malononitrile radical to the octenes.

The two pairs are also contrasted by their stereochemical outcomes. Additions to the phenylpropenes (entries 1,2) were not stereospecific (as required by an iodonium ion mechanism), but they were reasonably stereoselective. Both the *E* and *Z* isomers gave the same adducts **8a** in the same ratio (6/1).[10] This ratio held constant throughout the early and middle parts of the reaction, but began to fall as the conversion increased to 80-90%. As soon as the starting iodomalononitrile was consumed, the products isomerized very rapidly to what we assume is the equilibrium mixture (1/1.1). The isomerizations probably occur by degenerate iodine transfer.[11] The additions to the octenes (entries 3,4) were almost completely non-selective; however, there was just enough selectivity for us to safely conclude that the *E* and *Z*-isomers again give the same kinetic product. As with the styrenes, this kinetic products **8b** began to isomerize at late conversions to a thermodynamic ratio that was very slightly different from the kinetic ratio.

Since the atom transfer addition reactions are not stereospecific, we conclude that the ionic mechanism proceeding through an iodonium ion is not operative. Instead, the results indicate that *E* and *Z* alkenes proceed to a common intermediate. This is nicely consistent with the radical mechanism, and it indicates that iodine transfer to the benzylic radical **10a** is stereoselective, but atom transfer to a related alkyl-substituted radical **10b** is not stereoselective. To confirm that the stereoselectivity was indeed the result of 1,2 asymmetric induction in a radical reaction, we reduced a 1/1.1 mixture of benzylic iodides **8a** under standard conditions with tributyltin deuteride. From this reaction we isolated a mixture of mono-deuterated products **13** in a ratio of 4/1.[12] The configuration of the major isomer of **13** was readily assigned as syn by a combination of proton decoupling and noe experiments.[13]



8a (1/1) **13**-syn (4/1) **13**-anti **eq 4**



Model

These observations are nicely consistent with an emerging model for 1,2-asymmetric induction that is shown above.[5] This model predicts that good levels of asymmetric induction will be observed when the stereocenter adjacent to the radical is influenced by A-strain and when the sizes of the substituents on this carbon are significantly different. A-Strain is important because it restricts the number of low energy rotamers available to the radicals (the small hydrogen must reside near the phenyl group). When the phenyl group is replaced by an alkyl group, A-strain is lost, and the stereoselectivity in the atom transfer reactions disappears. We are confident in assigning the configuration of the major isomer of the benzylic iodide **8a** as syn by analogy to **13**.

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References and Notes

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3. a) Curran, D. P.; Chen, M.-H; Spletzer, E.; Seong, C. M.; Chang, C.-T. *J. Am. Chem. Soc.* **1989**, *111*, 8872. b) Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140.
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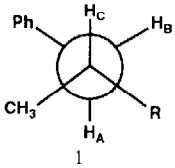
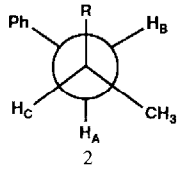
5. a) Hart, D. J. Huang, H.-C.; Krishnamurthy, R.; Schwartz, T. *J. Am. Chem. Soc.* **1989**, *111*, 7507. b) Porter, N. A.; Giese, B.; Curran, D. P. *Acc. Chem. Res.*, submitted. c) Hart, D. J., Krishnamurthy, R. *Synlett*, **1991**, 425.
6. Radical **10** might also abstract iodine from I_2, which can be visually detected in the reaction mixture.
7. Curran, D. P.; Morgan, T. M.; Schwartz, E.; Snider, B. B.; Dombroski, M. A. *J. Am. Chem. Soc.* **1991**, *113*, 6607.
8. Protons for *E* and *Z* 4-octene are not well separated at 300 MHz. However, the protons for the diiodides **11** were. Since each reaction produced only one diiodide, this rules out alkene isomerization.
9. Leading references. a) Zanger, M.; Rabinowitz, J. L. *J. Org. Chem.* **1975**, *40*, 248. b) Ayres, R. L.; Michejda, C. J.; Rack, E. P. *J. Am. Chem. Soc.* **1971**, *93*, 1389.
10. ^{1}H NMR data of **8a** ($CDCl_3$); major: δ 7.56-7.16 (5 H, m), 5.39 (1 H, d, *J* = 6.5 Hz), 2.06 (1 H, quint, *J* = 6.5 Hz), 1.78 (3 H, s), 1.53 (3 H, d, *J* = 6.5 Hz); minor: δ 7.56-7.16 (5 H, m), 5.83 (1 H, d, *J* = 3.9 Hz), 2.65 (1 H, dq, *J* = 7.0, 3.9 Hz), 1.75 (3 H, s), 1.65 (3 H, d, *J* = 7.0 Hz).
11. Newcomb, M.; Curran, D. P. *Acc. Chem. Res.* **1988**, *21*, 201.
12. A related stereoselective hydrogen transfer has recently been reported. Giese, B.; Bulliard, M.; Zeitz, H.-G. *Synlett* **1991**, 412.
13. The three low energy rotamers of **13** (lacking deuterium) are shown below. Proton couplings rule out significant contribution of rotamer 3, while noe experiments are only consistent with rotamer 1. This analysis is to assign the benzylic protons.



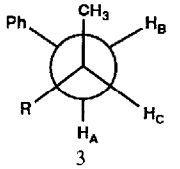
1

R = $C(CN)_2Me$



2

Not consistent with noe



3

Not consistent with coupling constants

H_A δ = 2.47 J_{AC} = 11.4 Hz, exhibits large noe when CH_3 is irradiated

H_B δ = 3.21 J_{BC} = 2.9 Hz, exihibits no noe when CH_3 is irradiated

On treatment of **8a** with Bu3SnD, H_A is selectively replaced by deuterium.

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