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N-Phenyltriazolinedione as an initiator in the radical addition of thiophenol to alkenes

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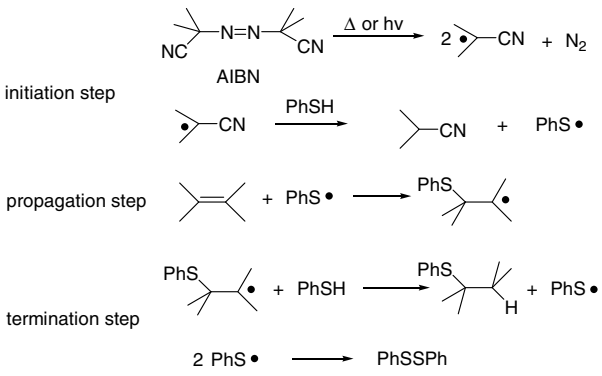
ABSTRACT

N-Phenyltriazolinedione is found to be an efficient initiator in the radical (*anti*-Markovnikov) addition of thiophenol to 2-methyl-2-butene. A second, minor, product (an alcohol, from oxygen addition) was also obtained, and a possible mechanistic scheme is proposed.

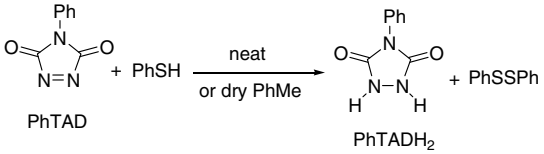
Thiol addition to alkenes is a well-known reaction[1] that takes place at room temperature, upon heating,[2] or under UV irradiation[3] in a radical mode, shows an *anti*-Markovnikov regioselectivity,[1,4] and finds many synthetic applications.[5] Initiators are also used in the reaction, and 2,2′-azobis(1-methylpropionitrile), AIBN, is one of the most frequently chosen ones.[6] The action of AIBN as initiator is, in the most simplified way, as shown in Scheme 1.

Initial homolytic decomposition of AIBN liberates a N_2 molecule, and gives rise to two isobutyronitrile carbon-centered radical, that abstract two hydrogen atoms from two molecules of thiophenol and thus create two reactive thiophenoxy radicals, PhS·, during the initiation step of the reaction. This adds to the double bond of an alkene in an *anti*-Markovnikov mode and produces a carbon-centered radical in the propagation step. Finally, this radical abstracts a hydrogen atom from a thiophenol molecule in the termination step, reproducing a thiophenoxy radical which continues the propagation step. A combination of two thiophenoxy radicals also contributes to the termination step.

4-Substituted-1,2,4-triazoline-3,5-diones, TADs, are compounds of high reactivity toward cycloadditions[7] and ene reactions.[8] They are prepared via an oxidation reaction from their precursor urazoles,[9] and their chemistry attracts research interest from both the synthetic[10] and mechanistic[11] points of view. Recently, we reported on the ability of 4-phenyl-1,2,4-triazoline-3,5-dione, PhTAD, to dimerize thiols to disulfides in excellent yields, Scheme 2.[12] Since TADs are cyclic diazo compounds, we decided to test PhTAD as an initiator in radical additions to alkenes. We report here on PhTAD acting as an initiator in the radical addition of thiophenol to 2-methyl-2-butene. To our knowledge this is a new aspect of TAD reactivity.



Scheme 1. AIBN as an initiator in the radical addition of thiophenol to alkenes.



Scheme 2. Reduction of PTAD to the parent urazole and oxidation of PhSH to the diphenyl-disulfide.

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Solid PhTAD (2% molar ratio with regard to the alkene) was added at room temperature to a freshly prepared solution of 2-methyl-2-butene and PhSH in dry PhMe. After 10 min of stirring, the addition product phenyl alkyl sulfide **1** and diphenyl disulfide, Ph_2S_2, were detected by TLC and by GC MS. This was verified also by ^{1}H NMR spectroscopy of the crude reaction mixture after removal of the excess PhSH and phenylurazole by washing the solution with cold 1 N NaOH or KOH solution, and removal of the solvent. The ene addition product, between PhTAD and the alkene, was also formed in appreciable amounts.

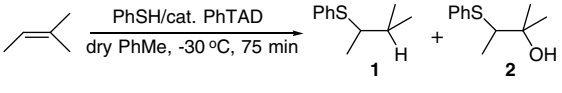
We then studied the reaction with respect to the molar ratio of the reagents, reaction temperature and time, and solvent quantity. The best conditions found were a temperature of −30 °C, with a molar ratio of alkene:PhTAD:PhSH equal to 50:1:50, in an equal volume solution of PhSH and dry PhMe, Scheme 3. Under the above-mentioned conditions, the best molar ratio of [sulfide **1**]:[Ph_2S_2] was found to be equal to unity, and no ene product was detected. When the reaction was performed under the above-mentioned experimental conditions in the absence of PhTAD, only diphenyldisulfide was detected as the product by TLC, GC MS, and ^{1}H NMR.

Preparative TLC (*n*-hexane or pentane/EtOAc 30:1 v/v) afforded sulfide **1** in 5% yield and hydroxy-sulfide **2** in 0.7% yield, with regard to the starting alkene (i.e., molar ratio [**1**]/[**2**] ∼ 7:1), which were characterized by NMR spectroscopy and HRMS.[13]

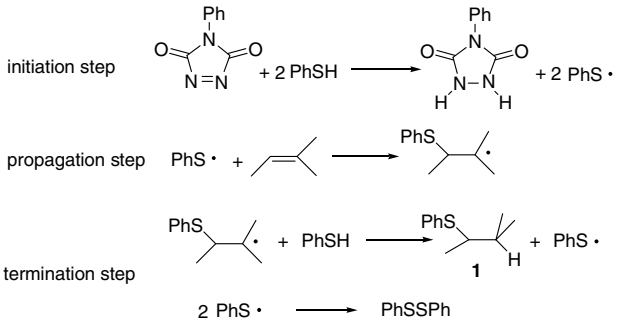
Since all of the above reactions were performed in scattered light (lights in the vicinity were turned off during the experiments), we also ran the reaction in the dark. It is known that light itself promotes the addition of thiophenol to alkenes.[1] We found that in the dark, at room temperature, and for the same reaction time (75 min), the formation of the disulfide diminished dramatically, the molar ratio [sulfide **1**]:[Ph_2S_2] rose to 3:1, and the molar ratio [**1**]/[**2**] was ∼15:1, as was judged from the ^{1}H NMR of the crude mixture. Again, in the absence of PhTAD no products **1** or **2** were detected except for diphenyl disulfide during the above-mentioned period of time. We decided to take advantage of this time window to increase, if possible, the isolated yield of product **1**. Under the above-mentioned conditions, we ran the reaction by changing the quantity of PhTAD and isolated the product **1** by preparative TLC (with *n*-hexane as eluent). An almost linear increase of the % yield of the isolated product **1** on going from 5% yield with 50:1:50 molar ratio to 14% yield with 50:2:50, and 21% with 50:5:50 molar ratio of alkene:PhTAD:PhSH was found.[14] By further increasing the quantity of PhTAD a plateau was encountered for the % yield of product **1**. By changing the molar ratio from 50:9:50 to 50:25:50, the yield was close to 16%. All isolated yields are quoted with regard to the starting alkene. In addition, higher concentrations of diphenyl disulfide were observed in these experiments. In all the experiments the molar ratio [**1**]/[**2**] remained almost unchanged, revealing a different formation pathway for product **2**.

Taking together the above findings, we propose the following mechanistic scheme for the studied reaction, Scheme 4.

According to the above scheme, PhTAD abstracts two hydrogen atoms from two molecules of PhSH, giving rise to the formation of the parent urazole and two thiophenoxy radicals in the initiation step. The process then continues as discussed above (Scheme 1). In the light of the above proposed mechanistic scheme, when the molar ratio of PhTAD is increased, the concentration of thiophenoxy radicals is high enough to give more dimerization product, as was found experimentally. Furthermore, PhTAD could be recycled from the resulting *N*-phenylurazole, isolated by filtration from the reaction mixture, via known oxidation reactions.[9]



Scheme 3. Addition of PhSH to 2-methyl-2-butene with PhTAD as an initiator in catalytic quantities.

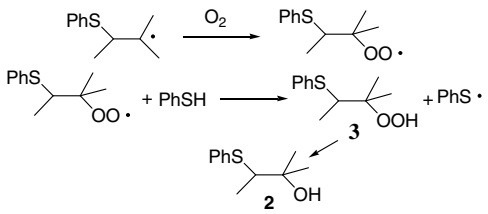


Scheme 4. A possible mechanistic scheme for the radical addition of PhSH to 2-methyl-2-butene, with PhTAD as initiator.

Formation of compound **2**, is in accordance with a radical reaction sequence, since it could be produced by trapping of the carbon-centered radical by traces of O_2 in the reagents or solvent, resulting in a peroxide intermediate **3**, which could then decompose to the final hydroxy-sulfide **2**, Scheme 5.

Hydroxy-sulfides with similar structures have been reported to be formed as secondary products during thiol radical addition to alkenes under continuous flow of O_2.[15] Thus, we decided to test the above reaction in the presence of pure oxygen. We ran the reaction in the dark, at room temperature with the same molar ratio of reactants and solvent quantity, and bubbling with pure O_2 for 75 min. After the usual work-up, the ^{1}H NMR spectrum of the crude reaction mixture showed the presence of an additional quartet centered at 3.66 ppm (the corresponding quartet for sulfide **1** resonates at 3.22 ppm, whereas that of hydroxy-sulfide **2** appears at 3.25 ppm). Upon addition of triphenylphosphine to the NMR tube, the above quartet vanished and hydroxy-sulfide **2** was then evident. We interpret this result as evidence for the formation of hydroperoxide **3**, in higher quantities in the presence of oxygen, and that in the presence of PPh_3 it is reduced to the hydroxy-sulfide **2**.

A comment should be made at this point with respect to the smoother reactivity (low temperatures, dark conditions) of PhTAD with regard to AIBN (higher temperatures, irradiation), as a radical initiator. Despite the fact that PhTAD is a cis-locked azo-compound, its action has some major differences on bond dissociation energy grounds. In the case of PhTAD: a weak N=N double bond has to open homolytically together with two, overall, weak S–H bonds, Scheme 4. This energy demand is satisfied by the formation of two N–H bonds in the urazole molecule. With AIBN, two strong C–N bonds have to break (high energy demand) and a weak triple N≡N bond is the energy gain, Scheme 1. We are of the opinion that such energy differences give PhTAD the opportunity to act as an initiator in an easier way with regard to AIBN.



Scheme 5. Possible pathway for the formation of hydroxy-sulfide **2**.

We have reported here a new feature of PhTAD, which was found to act as an initiator in the radical addition of thiophenol to 2-methyl-2-butene. PhTAD could be recycled from the reaction by oxidation of the urazole formed. The reaction was found to work under conditions where no addition product was observed in the absence of PhTAD. A hydroxy-sulfide was also isolated in minor amounts, testifying to the radical nature of the addition reaction. Further studies on clarification of the mechanistic profile of the reaction are underway.

Acknowledgments

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References and notes

1. Griesbaum, K. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 273–287.
2. Jarvis, B. B. *J. Org. Chem.* **1970**, *35*, 924–927.
3. Brown, H. C.; Kawakami, J. H.; Liu, K.-T. *J. Am. Chem. Soc.* **1973**, *95*, 2209–2216.
4. (a) Skell, P. S. *Organic Reaction Mechanisms*; Special Publication No. 19, The Chemical Society, London, 1965; (b) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 753–764.
5. (a) Bachi, M. D.; Korshin, E. E.; Ploypradith, P.; Cumming, J. N.; Xie, S.; Shapiro, T. A.; Posner, G. H. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 903–908; (b) Bilokin, Y. V.; Melman, A.; Niddam, V.; Benhamu, B.; Bachi, M. D. *Tetrahedron* **2000**, *56*, 3425–3437; (c) Korshin, E. E.; Hoos, R.; Szpilman, A. M.; Konstantinovski, L.; Posner, G. H.; Bachi, M. D. *Tetrahedron* **2002**, *58*, 2449–2469.
6. (a) Parsons, A. F. *An Introduction to Free Radical Chemistry*; Blackwell Science Ltd, 2000; (b) Fossey, J.; Fefort, D.; Sorba, J. *Free Radicals in Organic Chemistry*; John Wiley & Sons, 1995.
7. (a) Breton, G. W.; Newton, K. A. *J. Org. Chem.* **2000**, *65*, 2863–2869; (b) Henderson, A. P.; Mutlu, E.; Leclercq, A.; Bleasdale, C.; Clegg, W.; Henderson, R. A.; Golding, B. T. *Chem. Commun.* **2002**, 1956–1957; (c) Jensen, F.; Foote, C. S. *J. Am. Chem. Soc.* **1987**, *109*, 6376–6385.
8. (a) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 556–577; (b) Erden, I.; Song, J.; Cao, W. *Org. Lett.* **2000**, *2*, 1383–1385; (c) Adam, W.; Griesbeck, A. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1070–1071; (d) Khazaei, A.; Zolfigol, M. A.; Rostami, A. *Synthesis* **2004**, 2959–2961; (e) Joshi, A. V.; Bhusare, S.; Baidossi, M.; Qafisheh, N.; Sasson, Y. *Tetrahedron Lett.* **2005**, *46*, 3583–3585; (f) Ali, M. H.; McDermott, M. *Tetrahedron Lett.* **2002**, *43*, 6271–6273; (g) Patel, S.; Mishra, B. K. *Tetrahedron Lett.* **2004**, *45*, 1371–1372; (h) Leino, R.; Lönnqvist, J.-E. *Tetrahedron Lett.* **2004**, *45*, 8489–8491; (i) Laszlo, P.; Delaude, L. *J. Org. Chem.* **1996**, *61*, 6360–6370; (j) Peskin, A. V.; Winterbourn, C. C. *Free Radical Biol. Med.* **2001**, *30*, 572–579; (k) Hajipour, A. R.; Mallakpour, S. E.; Adibi, H. *Phosphorous, Sulfur Silicon* **2002**, *177*, 2277–2284; (l) Hajipour, A. R.; Mallakpour, S. E.; Adibi, H. *J. Org. Chem.* **2002**, *67*, 8666–8668; (m) Hajipour, A. R.; Mallakpour, S. E.; Adibi, H. *Sulfur Lett.* **2002**, *25*, 155–160; (n) Akdag, A.; Webb, T.; Worley, S. D. *Tetrahedron Lett.* **2006**, *47*, 3509–3510; (o) Barton, D. H. R.; Hesse, R. H.; O'Sullivan, A. C.; Pechet, M. M. *J. Org. Chem.* **1991**, *56*, 6697–6702; (p) Brzezinska, E.; Ternay, A. L., Jr. *J. Org. Chem.* **1994**, *59*, 8239–8244; (q) Schönhert, H.; Ringsdorf, H. *Langmuir* **1996**, *12*, 3891–3897.
9. (a) Read, G.; Richardson, N. R. *J. Chem. Soc., Perkin Trans. 1* **1996**, 167–174; (b) Cookson, R. C.; Gupte, S. S.; Stevens, I. D. R.; Watts, C. T. *Org. Synth.* **1971**, *51*, 121–127; (c) Menard, C.; Doris, E.; Mioskowski, C. *Tetrahedron Lett.* **2003**, *44*, 6591–6593; (d) Zolfigol, M. A.; Zebarjadian, M. H.; Chehardoli, G.; Mallakpour, A. E.; Shamsipur, M. *Tetrahedron* **2001**, *57*, 1627–1629; (e) Zolfigol, M. A.; Torabi, M.; Mallakpour, S. E. *Tetrahedron* **2001**, *57*, 8381–8384; (f) Zolfigol, M. A.; Nasr-Isfahani, H.; Mallakpour, S.; Safaiee, M. *Synlett* **2005**, 761–764.
10. (a) Radl, S. *Adv. Heterocycl. Chem.* **1996**, *67*, 119–205; (b) Clennan, E. L. *Tetrahedron* **2000**, *56*, 9151–9179; (c) Johannsen, M.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689–1708; (d) Corey, E. J.; Snider, B. B. *Tetrahedron Lett.* **1973**, *35*, 3091–3094; (e) Adam, W.; Degen, H.-G.; Krebs, O.; Saha-Moller, C. R. *J. Am. Chem. Soc.* **2002**, *124*, 12938–12939; (f) Baran, P. S.; Guerrero, C. A.; Corey, E. J. *Org. Lett.* **2003**, *5*, 1999–2000; (g) Baran, P. S.; Guerrero, C. A.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 5628–5629; (h) Adam, W.; Pastor, A.; Wirth, T. *Org. Lett.* **2000**, *2*, 1295–1297.
11. (a) Cheng, C. C.; Seymour, C. A.; Petti, M. A.; Greene, F. D.; Blount, J. F. J. *J. Org. Chem.* **1984**, *49*, 2910–2916; (b) Orfanopoulos, M.; Smonou, I.; Foote, C. S. *J. Am. Chem. Soc.* **1990**, *112*, 3607–3614; (c) Chen, J. S.; Houk, K. N.; Foote, C. S. *J. Am. Chem. Soc.* **1997**, *119*, 9852–9855; (d) Singleton, D. A.; Hang, C. *J. Am. Chem. Soc.* **1999**, *121*, 11885–11893; (e) Syrgiannis, Z.; Elemes, Y. *Tetrahedron Lett.* **2006**, *47*, 6831–6834; (f) Syrgiannis, Z.; Elemes, Y. *Tetrahedron Lett.* **2006**, *47*, 2961–2964; (g) Elemes, Y.; Stratakis, M.; Orfanopoulos, M. *Tetrahedron Lett.* **1997**, *38*, 6437–6440; (h) Elemes, Y.; Orfanopoulos, M. *Tetrahedron Lett.* **1991**, *32*, 2667–2670; (i) Orfanopoulos, M.; Elemes, Y.; Stratakis, M. *Tetrahedron Lett.* **1989**, *30*, 4875–4878; Vassilikogiannakis, G.; Elemes, Y.; Orfanopoulos, M. *J. Am. Chem. Soc.* **2000**, *122*, 9540–9541.
12. Christoforou, A.; Nicolaou, G.; Elemes, Y. *Tetrahedron Lett.* **2006**, *47*, 9211–9213.
13. *Spectroscopic data for* **1**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.20–7.60 (m, 5H), 3.22 (dq, 1H, J = 4.4 Hz, J = 6.9 Hz), 1.93 (dseptet, 1H, J = 4.4 Hz, J = 6.9 Hz), 1.27 (d, 3H, J = 6.9 Hz, CH_3–C–S), 1.05 (d, 3H, J = 6.9 Hz), 1.04 (d, 3H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 60 MHz) δ 131.5, 129.1, 128.8, 127.6, 127.2, 126.4, 50.1 (CH–S), 32.5 ($CHMe_2$), 20.1, 18.3, 17.1 (CH_3–C–S); HRMS calculated $C_{11}H_{16}S$: 180.3101, found: 180.0976. Spectroscopic data for **2**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.20–7.60 (m, 5H), 3.25 (q, 1H, J = 7.0 Hz), 2.52 (br s, 1H, –OH), 1.38 (d, 3H, J = 7.0 Hz), 1.32 (s, 3H), 1.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 60 MHz) δ 135.9, 131.7, 129.0, 126.9, 73.0 (C–O), 58.3 (CH–S), 27.2, 25.6, 18.4 (CH_3–C–S); HRMS calculated $C_{11}H_{16}OS$: 196.3095, found: 196.0915.
14. *Typical experimental procedure*: In a flame-dried 10 mL tube bearing a screw cap flushed with Ar and wrapped with aluminum foil, a solution of PhSH (0.59 mL, 5.7 mmol) in dry PhMe (0.59 mL) was prepared at rt in the dark. To this solution 0.6 mL (5.7 mmol) of 2-methyl-2-butene was added, immediately followed by the addition of a catalytic quantity of solid PTAD (i.e., 100 mg, 0.57 mmol) in one portion. After 75 min of stirring at rt, the solution was washed three times with cold 1 N NaOH or KOH to remove unreacted PhSH and urazole, the organic layer was dried with Na_2SO_4, and after filtration, the solvent was removed on a rotary evaporator. The remaining crude product was chromatographed on preparative TLC plates, eluent: *n*-hexane, affording pure product **1** as a pale yellow liquid (216 mg, 21%), and traces of compound **2** (7 mg, 0.6%) with regard to the starting alkene.
15. (a) Iriuchijima, S.; Maniwa, K.; Sakakibara, T.; Tsuchihashi, G.-I. *J. Org. Chem.* **1974**, *39*, 1170–1171; (b) Szmant, H. H.; Mata, A. J.; Namis, A. J.; Panthananickal, A. M. *Tetrahedron* **1976**, *32*, 2665–2680.