Synthesis, Structure, and Reactivity of 1,4-Diaryl-2-(arylamino)but-2-ene-1,4-diones

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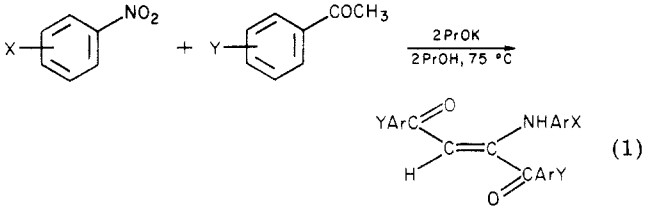
The one-pot synthesis of the title compounds (1) is achieved by reacting acetophenones and nitrobenzenes in 2-propanol with potassium 2-propoxide. The stereochemistry of the 2-butenes has been determined to be *Z* from an X-ray analysis. Hydrolysis and reaction with hydrazine are reported as examples of the reactivity of the title compounds.

1,4-Diketones are useful starting materials for the synthesis of a number of heterocycles.[1] The but-2-ene-1,4-dione system and its functionalized derivatives are potentially even more valuable. Their use[2] has, however, been limited because of their relatively difficult synthesis.

We have developed a very simple, one-pot synthesis leading to 1,4-diaryl-2-(arylamino)-but-2-ene-1,4-diones (1, ArC(O)C(NHAr)=CHC(O)Ar). The determination of the configuration around the double bond and examples of the reactivity of 1 are also described in this paper.

Results and Discussion

Synthesis of 1,4-Diaryl-2-(arylamino)but-2-ene-1,4-diones. Addition of potassium 2-propoxide to a boiling solution of variously substituted acetophenones and nitrobenzenes in 2-propanol gives, after 1–2 h at reflux, compound 1 in fair to good amounts (eq 1). The actual



(1)

1a, X = Y = H
b, X = H; Y = *p*-Cl
c, X = *p*-Cl; Y = H
d, X = Y = *p*-Cl
e, X = *p*-CMe; Y = H

yields, which depend on the nature and the number of substituents, are reported in Table I, together with relevant analytical data.

The yields reported, although not optimized, are admittedly not very high. Alternative syntheses[3,4] require the addition of anilines to dibenzoylacetylenes which can be synthesized only in three or four steps.[5,6] The overall yields[3,4] are therefore not much different from those reported in Table I for our one-step synthesis. The identitiy of **1b** (X = H, Y = *p*-Cl) has also been checked by ^{13}C NMR analysis (two carbonyl-type carbons are evident at δ 193.6 and 191.6 from Me_4Si as an internal standard in $CDCl_3$). The IR spectrum in KBr shows all five characteristic peaks between 1550 and 1665 cm^{-1} reported[3] for the same compound synthesized by a different route.[3,4]

These data, however, do not allow one to establish the stereochemistry about the double bond. The ^1H NMR data (see Table I) for the vinylic proton show that all the compounds obtained have the same stereochemistry but do not allow one to say whether the vinylic hydrogen is cis to the carbonyl or to the anilino group. References in the literature are contradictory, both *E*[3] and *Z*[4,7,8] configurations being reported for what appears, from the analytical data, to be the same compound we have obtained

Table I. Yields and Analytical Data for XArC(O)CH=C(NH—Ar—Y)C(O)ArX

X	Y	mp, °C (solvent)	yield, %[a,b]	^1H NMR[c]	ref
H	H	128-129 (MeOH/$CHCl_3$)	46	6.05	*d*
H	*p*-Cl	149-150 (MeOH/$CHCl_3$)	44	6.10	*e*
p-Cl	H	170-171 (*i*-PrOH/$CHCl_3$)	40	6.06[f]	
p-Cl	*p*-Cl	235-236 (Me_2CO/$CHCl_3$)	81	6.06[g]	
p-OMe	H	135-136 (MeOH)	32	5.96	*h*

[a] These are yields of isolated compound after recrystallization. [b] Satisfactory analytical data were reported for all new compounds listed in the table. [c] This is the chemical shift of the vinyl hydrogen, in $CDCl_3$, from Me_4Si as an internal standard. [d] See ref 4. [e] See ref 3. [f] Mass spectrum (70 eV), *m/e* 397, 395 (M), 256 (100%), 139, 111, 77. [g] Mass spectrum (70 eV), *m/e* 433, 431, 429 (M), 290 (100%), 139, 111, 75. [h] Dupont, G. *Bull. Soc. Chim. Fr.* **1927**, *41*, 1167.

Table II. Selected Bond Distances and Angles for Compounds 1a[a]

bond distances, A	angles, deg
C(1)-O(1), 1.242 (3)	O(1)-C(1)-C(2), 121.9 (3)
C(1)-C(2), 1.437 (4)	C(1)-C(2)-C(3), 123.2 (3)
C(2)-C(3), 1.365 (4)	C(2)-C(3)-C(4), 118.1 (3)
C(3)-C(4), 1.515 (4)	C(2)-C(3)-N, 123.2 (3)
C(3)-N, 1.345 (4)	C(4)-C(3)-N, 112.7 (3)

[a] See Figure 1.

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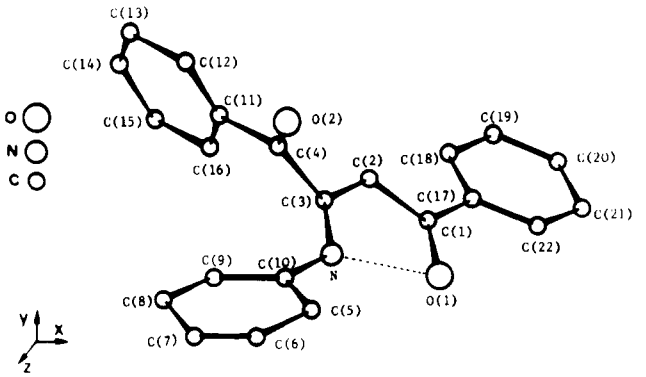
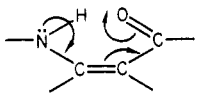


Figure 1. 1,4-Diphenyl-2-(phenylamino)but-2-ene-1,4-dione as viewed along the *c* axis.

in this work. We have therefore unambiguously determined the structure of **1a** (X = H, Y = H) by X-ray analysis.

Structure of 1a. Three-dimensional X-ray analysis (see Experimental Section) indicates for compound **1a** the structure shown in Figure 1, in which the molecule is viewed along the *c* axis. Relevant angles and distances are collected in Table II. The main features are as follows: (i) the two carbonyls are on opposite sides of the carbon–carbon double bond (*Z* configuration); (ii) the three aromatic rings are all out of the carbon–carbon double bond plane (by 50.0, 68.3, and 29.6°); (iii) the short distance between the nitrogen and the carbonyl oxygen (2.66 Å) clearly indicates the existence of hydrogen bonding between the NH and the CO(1) groups; (iv) the bond distances show the expected values for a system in which the NH moiety, the carbon–carbon double bond, and one of the two carbonyls interact as shown in **2**. The second



2

carbonyl and the phenyl rings are not involved in this kind of interaction as shown by the following distances: N–H···O(1) 2.66 Å, N–H···O(2) = 2.91 Å; O(1) and O(2) are 0.22 and 1.12 Å from the ethylenic plane, respectively.

Mechanism of Formation of Compounds 1. We know from previous work[9] that nitrobenzenes are easily reduced in boiling 2-propanol in the presence of potassium 2-propoxide to give azoxy and aniline compounds. Nitrosobenzene is the first intermediate in the reduction of nitrobenzene.[9] We therefore suspected that **1** might also be formed by reaction of nitrosobenzene with the added ketone. In fact, reaction of *p*-chloronitrosobenzene with acetophenone under our usual conditions led to isolation of a substantial amount (16%) of **1c** together with the expected[9,10] *p,p'*-dichloroazoxybenzene and *p,p'*-dichloroazobenzene.

Condensation of nitrosobenzene with compounds containing "active" CH bonds has been reported to give nitrones.[11] The expected nitrone, in our case an acyl nitrone, is believed not to be stable enough to be isolated under our reaction conditions. We have synthesized it by modifying a reported procedure[12] involving reaction of nitrosobenzene and phenacylpyridinium bromide in slightly basic solutions as shown in eq 2.

Scheme I

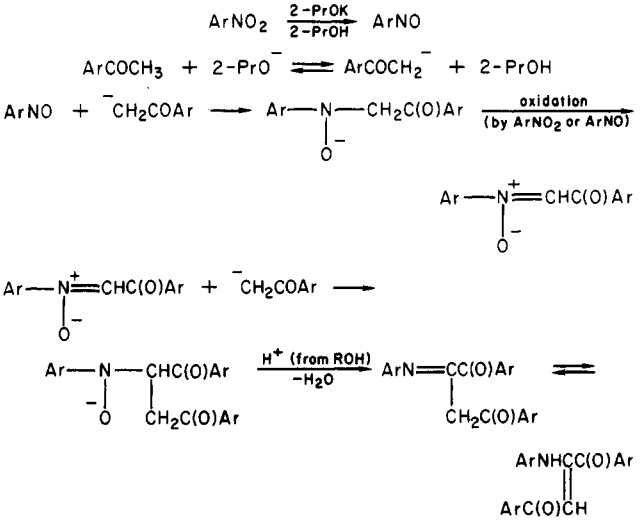
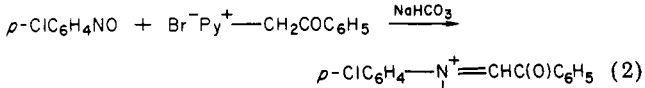


Table III. Yields and Analytical Data for XArC(O)CH$_2$C(O)C(O)ArX As Obtained from Hydrolysis of Compounds 1a–e[a]

starting matl	X	mp (EtOH), °C	reaction time, min	yield,[b] %
1a	H	104–106	40	97[c,d]
1c	H		40	90
1b	*p*-Cl	160–162	40	97[c,e]
1d	*p*-Cl		40	99
1e	*p*-OCH$_3$	127–129	80	95[f]

[a] In dioxane/aqueous 4 M HCl (3:1) at reflux. [b] Of isolated material. [c] Satisfactory analytical data were reported for all new compounds listed in the table. [d] Mass spectrum (70 eV), *m/e* 252 (M), 224, 147 (100%), 105, 77, 69. [e] Mass spectrum (70 eV), *m/e* 294, 292 (M – CO), 181 (100%), 139, 111, 75, 69. [f] Mass spectrum (70 eV), *m/e* 312 (M), 284, 177, 135 (100%), 92, 77, 69. Anal. Calcd: C, 69.23; H, 5.13. Found: C, 68.39; H, 5.19.



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Reaction of **3** with acetophenone in the presence of potassium 2-propoxide in 2-propanol gives **1c** in a substantial yield (55%). The mechanism for the formation of compound **1** may therefore be sketched as in Scheme I. The detailed mechanism of nitro to nitroso reduction is currently under investigation.[9] The base-catalyzed condensation of nitrosobenzene with acetophenone proceeds according to a known reaction pathway,[11,12] whereas condensation of the acetophenone enolate with the nitrone follows the expected reaction mechanism for attack of a nucleophile on nitrones.[13] Isolation of only one stereoisomer of **1** shows that our product is the thermodynamically stable one; this is in agreement with the position of known equilibria of the imine ⇄ enamine type.[14]

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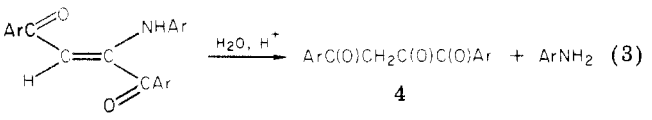
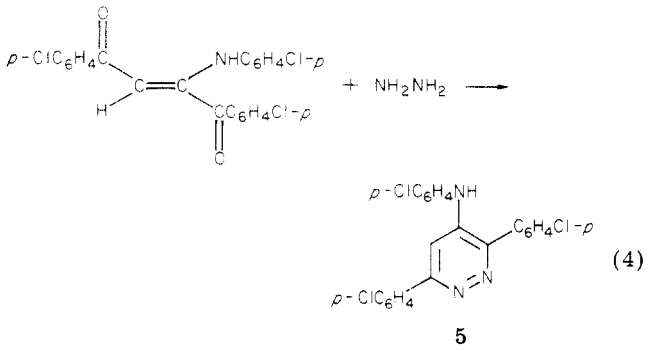
In the last part of the paper we will briefly discuss some reactions of 1.

Hydrolysis of 1. Diketo enamines 1 may be easily hydrolyzed both in basic and acidic solutions, the acid-catalyzed reaction being, as expected,[15] faster. The hydrolysis products, obtained in virtually quantitative yield, are of the butane-1,2,4-trione type. They may exist as equilibrium mixtures of enol and keto forms.[16] ^{1}H NMR spectra show signals at δ 6.8–6.9 ($CDCl_3$ from Me_4Si) attributed to the vinylic proton of the enol, without trace of CH_2 protons. We made no attempt to evaluate the relative ratios of enol to keto forms, and, for the sake of simplicity, we will only consider the carbonyl form, with the understanding that no inference is being made about the position of the above equilibria. The hydrolysis products, formed according to eq 3 are described in Table III.



Compounds 4 are of interest in heterocyclic chemistry,[17] especially in furan chemistry, as well as for studies dealing with hydrogen bonding to carbonyls and solvent effects on these interactions.[16,18] The easy and unambiguous synthesis described above now makes this class of compounds readily available.

Reaction of 1 with Hydrazine. The but-2-ene-1,4-dione system reacts very easily with hydrazine, as expected.[19] In the single reaction we report here as an example (eq 4), the pyridazine 5 is obtained in 85% isolated yield. The fact that compound 5 is obtained starting from a diketobutene having a *Z* configuration shows that isomerization around the double bond occurs before cyclization, probably under basic catalysis by hydrazine. This kind of isomerization is known to occur in α,β-unsaturated carbonyls.[20]



Experimental Section

Synthesis of 1,4-Diaryl-2-(arylamino)but-2-ene-1,4-diones. General Procedure. After nitrobenzene (0.05 mol) and acetophenone (0.2 mol) are refluxed for 15 min in 2-propanol (100 mL), 100 mL of 0.5 M 2-PrOK in 2-PrOH is added at the rate needed to maintain reflux without external heating. The resulting brown solution is refluxed until reaction of the nitrobenzene is complete, as judged from TLC (Et_2O/petroleum ether; 1–2 h, depending on the substituents). The cooled solution is poured into water and carefully acidified with 1 M HCl. The brown solid which precipitates is filtered and washed with 2-propanol (once) and petroleum ether (several times). The bright yellow compound is then recrystallized from the appropriate solvent (see Table I). Compounds 1 may also be purified by column chromatography on silica gel by using ethyl ether/petroleum ether as the eluant.

The rates of reduction of nitrobenzenes are greatly reduced by the presence of oxygen.[9] Working at reflux ensures the expulsion of most of the air from the reaction mixture. The freeze–thaw procedure needed to completely remove oxygen is not justified by the increase in rates which could be obtained in the present reaction.

***p*-Chloronitrosobenzene.** The title compound has been synthesized by reducing *p*-chloronitrobenzene to (*p*-chlorophenyl)hydroxylamine (zinc dust in aqueous ammonium chloride solution) and oxidizing the crude hydroxylamine with iron trichloride in water at 3–5 °C. The nitroso compound is purified by steam distillation followed by recrystallization from methanol; mp 92–93 °C (lit.[21] mp 92–93 °C).

Reaction of *p*-Chloronitrosobenzene with Acetophenone. A solution of *p*-chloronitrosobenzene (0.075 g) in 2-PrOH (10 mL) containing acetophenone (0.3 mL) is added at 75 °C under nitrogen to 10 mL of 0.51 M 2-PrOK in 2-PrOH. After 2 min the reaction is quenched with solid carbon dioxide. Analysis by GLC (UCW 982, 250–290 °C) reveals the formation of **1c** (16%), *p,p'*-dichloroazoxybenzene (65%), and *p,p'*-dichloroazobenzene (18%).

***N*-(*p*-Chlorophenyl)-*C*-benzoylnitrone.** Phenacylpyridinium bromide in water (3 g in 10 mL) is added to a solution of *p*-chloronitrosobenzene (1.5 g in 100 mL of ethanol) kept at −8 °C. A solution of $NaHCO_3$ (0.82 g in 20 mL water) is then added dropwise under vigorous stirring, keeping the temperature below −5 °C. The color of the solution changes from green to pale yellow. After addition of cold water (100 mL), the reaction mixture is allowed to rest for 1 h. The solid collected by filtration is washed several times with cold water and then dissolved in ethyl ether (100 mL). The ether solution is dried (Na_2SO_4) and most of the solvent removed under reduced pressure. Addition of petroleum ether affords the compound as a solid: 0.65 g; mp 82–84 °C; the ^{1}H NMR [$CDCl_3$, Me_4Si; δ 7.4–7.9 (m, 9 H, aromatic), 8.3 (s, 1 H, CH=N)] is in agreement with the one reported[22] for *C*-benzoylnitrones; mass spectrum (70 eV), *m/e* 261, 259 (M^+), 243, 138, 105 (100%), 77.

Reaction of *N*-(*p*-Chlorophenyl)-*C*-benzoylnitrone with Acetophenone. A solution of nitrone (0.44 g) in 2-PrOH (6 mL) is added at 75 °C under stirring to 1 mL of 2-PrOK in 2-PrOH (1.02 M) containing acetophenone (0.3 mL). Quantitative GLC analysis (UCW 982, 290 °C) of the reaction mixture after 5 min gives a 55% yield of **1c**.

Hydrolysis of 1,4-Diaryl-2-(arylamino)but-2-ene-1,4-diones. The title reaction may be accomplished either under base or acid catalysis. The acid-catalyzed reaction which is faster and affords better yields, is conducted as follows. The dione (4 mmol) is dissolved in 40 mL of a 3:1 mixture dioxane/aqueous 4 M HCl and refluxed for 40–80 min, depending on the substituents (see Table III). Dilution with water is followed by extraction with ethyl ether. The ether layer is washed with HCl and then water and dried (Na_2SO_4), and the solvent is removed under reduced pressure to afford high yields (see Table III) of 1,4-diarylbutane-1,2,4-trione pure enough for synthetic purposes.

The basic hydrolysis [0.04 g of 1 in 20 mL of 2-PrOK (0.23 M) and 2 mL of water at reflux] has been followed by monitoring by GLC analysis the aniline formed. Yields up to 87% are obtained after 24 h.

Synthesis of 3,6-Bis(*p*-chlorophenyl)-4-(*p*-chloroanilino)pyridazine. (*Z*)-1,4-Bis(*p*-chlorophenyl)-2-(*p*-chloroanilino)but-2-ene-1,4-dione (0.7 g) is suspended in a solution of hydrazine (80%, 0.7 g) in 1:1 ethanol/acetic acid (60 mL). The mixture is refluxed until all the solid disappears (1.5 h), cooled, and poured into water. The white precipitate is filtered, washed with water, and recrystallized from 80% ethanol: yield 0.6 g

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(85%); mp 228–229 °C. Anal. Calcd C, 61.9; H, 3.3; Cl, 25.0; N, 9.8. Found: C, 61.6; H, 3.3; Cl, 25.0; N, 9.9. The ^{1}H NMR spectrum [$CDCl_3$, Me_4Si; δ 7–8.1 (m, 13 H, aromatics), 6.3 (br, 1 H, NH)] is consistent with the one reported for the unsubstituted arylpyridazine.[23]

X-ray Analysis. Crystals of **1a** ($C_{22}H_{16}NO_2$) are monoclinic: space group $P2_1/n$, a = 21.229 (5) Å, b = 13.632 (6) Å, c = 5.972 (8) Å; β = 94.1 (6)°, Z = 4, d_c = 1.26 g/cm^3, d_o = 1.24 g/cm^3. A total of 3031 intensities were collected on a Philips PW-1100 four-circle diffractometer (M Kα radiation) by using the θ–2θ scan method. The data have been analyzed by using the MULTAN program. The positional and anisotropic thermal parameters of all nonhydrogen atoms were refined by full-matrix least-square calculations. The resulting R factor is R = 0.060 for the 2095 reflections having $I \geq 3\sigma(I)$.

Supplementary Material Available: Final atomic thermal parameters, bond distances, and bond angles (4 pages). Ordering information is given on any current masthead page.

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Synthesis of (+)-(Neomenthylsulfonyl)methyl Isocyanide. Synthesis and Absolute Configuration of (*R*)-(+)-2-Methylcyclobutanone and (*S*)-(−)-2-Methylcyclobutanone†

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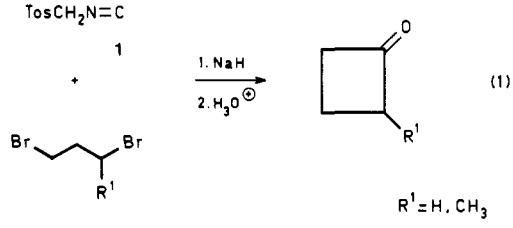
Menthol is used for the synthesis of optically pure (+)-(neomenthylsulfonyl)methyl isocyanide (NeSMIC, **8**), which is the first chiral sulfonylmethyl isocyanide reported. This NeSMIC is applied to a two-step synthesis of (*R*)-(+)-2-methylcyclobutanone (**12**), as well as its enantiomer (**11**), neither of which have been reported previously. The absolute configurations of **11** and **12** are determined by the octant rule and by an independent chiral synthesis.

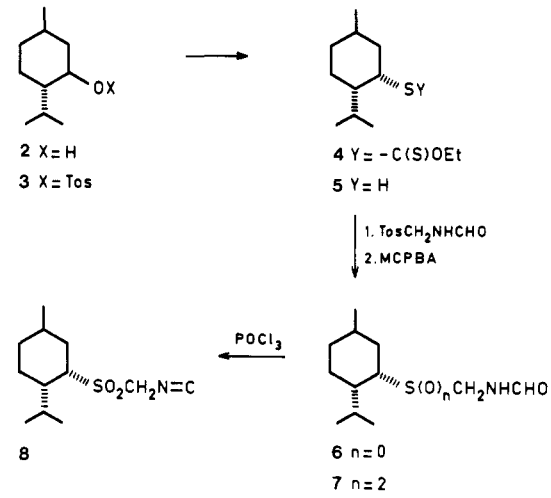
Umpolung reactions of sulfonylmethyl isocyanides have found useful synthetic applications.[1] For example, tosylmethyl isocyanide (TosMIC, **1**) is a formaldehyde (di)anion equivalent, which has been applied to the synthesis of several carbonyl compounds.[1,2] By this method an extremely simple synthesis of cyclobutanones was developed recently, which for $R^1 = CH_3$ leads to racemic 2-methylcyclobutanone (when racemic 1,3-dibromobutane is used, eq 1).[3]



The purpose of this paper is twofold: (a) to describe the first useful chiral analogue of TosMIC, i.e., (+)-(neomenthylsulfonyl)methyl isocyanide (NeSMIC, **8**), and (b) to initiate its application by the first synthesis of optically active 2-methylcyclobutanone, (−) as well as (+) (**11** and **12**, respectively, Scheme II). Moreover, **12** is prepared also from TosMIC and (*S*)-(+)-1,3-dibromobutane (eq 1), and the absolute configuration is determined to be *R*.

Synthesis of (+)-(Neomenthylsulfonyl)methyl Isocyanide (8). Several possibilities may be considered in designing chiral analogues of TosMIC.[4] For synthetically meaningful purposes[5] chirality preferably is introduced in the group R* of R*SO_2CH_2N=C by using optically pure and readily available starting materials.[6,7] The best results so far have been obtained with (−)-menthol.[8] By use of

Scheme I



essentially known chemistry, (−)-menthol (**2**) can be converted in six steps in 26% overall yield to (+)-(neo-

† Chemistry of Sulfonylmethyl Isocyanides 22. For part 21 see ref 2c.

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(5) Work describing synthetic applications based on asymmetric inductions with **8** is in progress.
(6) Chirality in compounds TosCHRN=C (R = alkyl, aryl; such compounds have indeed been prepared but were not resolved) will be lost via the conjugate bases, which are essential in most of their synthetic applications (see ref 1).
(7) Alternatively, partially resolved sulfoximinomethyl isocyanide PhSO(=NTos)CH_2N=C (mp 96 °C dec) was prepared and investigated previously: van Leusen, D., unpublished results, 1975–1977.

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