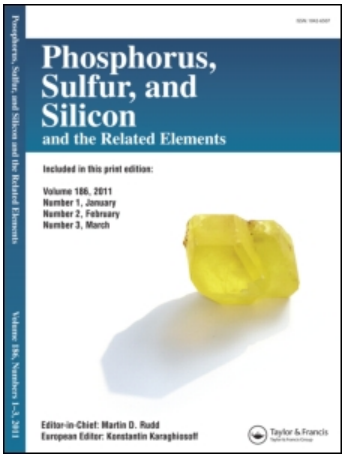

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ADDITION OF DIPHENYLPHOSPHINE TO MALEIC ANHYDRIDE AND RELATED COMPOUNDS

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A Michael addition of secondary phosphines to activated olefins containing the ethenedione moiety such as maleic anhydride, maleic ester and dibenzoylethene leads to functionalised tertiary phosphines. Reactions of activated olefins which contain a carboxylic group do not lead to the expected adducts; instead, phosphonium salts are formed by a sequence of reactions. A hydrogen shift plays a crucial role both in the reaction that leads to the adduct and in the reaction that leads to the phosphonium salt. Phosphinosuccinic anhydrides and phosphinosuccinic esters can be transformed into the corresponding succinic acids. Decarboxylation of phosphinosuccinic acids leads to phosphinopropionic acids.

Key words: Phosphine; maleic anhydride; phosphinosuccinic anhydride; phosphinosuccinic acid; phosphonium salt; decarboxylation.

INTRODUCTION

The addition of tertiary phosphines to systems with activated double bonds such as maleic anhydride and dibenzoylethene is a well-known reaction.[1,2] Phosphoranes are eventually obtained by rearrangement of an initially formed zwitterion. The base- or radical-catalysed addition of secondary phosphines to unsaturated systems such as acrylic esters is also well documented.[3–5] Arbusov *et al.*[6] have reported the addition of a primary phosphine to a maleic ester. Surprisingly, the addition of secondary phosphines to maleic anhydride and related compounds has not yet been reported. We considered this addition to be of interest as it would lead to new polyfunctional phosphines. Furthermore, we expected that the phosphinosuccinic anhydride ring could be opened with nucleophiles (amines, alcohols or water). In this way, a whole family of functionalised phosphinocarboxylic acids might become accessible.

RESULTS

We have found that an exotermic reaction occurs when diphenylphosphine is added to a solution of maleic anhydride (**1**) in chloroform. The resulting dark

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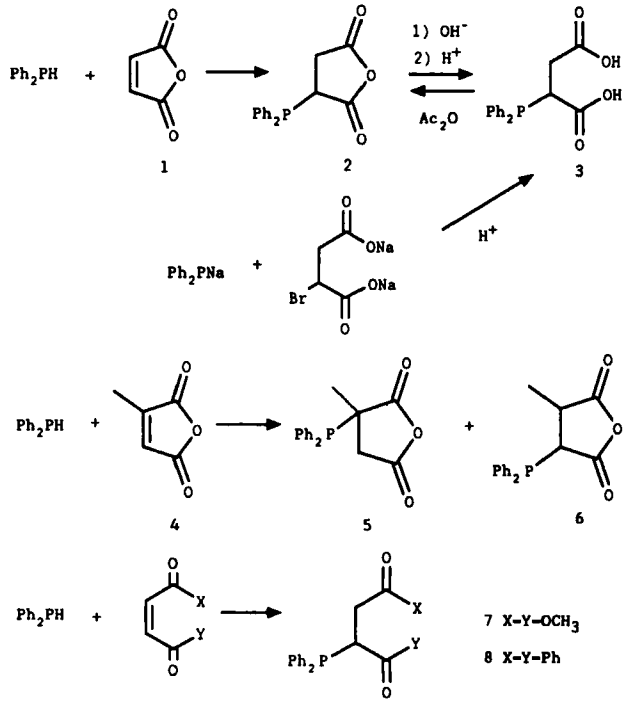
coloured solution contains many products that give rise to peaks in the +30 ppm region of the ^{31}P NMR spectrum. An acceptable yield of the desired addition product (**2**) is obtained only when the reaction is performed in tetrahydrofuran as the solvent and when a solution of (**1**) is added slowly, at room temperature, to a solution of diphenylphosphine. In this way, the spectroscopic yield of (**2**) is about 50%. Reaction at reflux temperature or with an excess of (**1**) leads to by-products. Prolonged reaction times at room temperature do not lead to an increase of the yield. However, the yield can be raised to ca. 70% by using an excess (50%) of the secondary phosphine. Apparently (**1**) partially enters into a competing reaction (polymerisation?[7]). it has been reported earlier[8] that dark-coloured by-products are formed upon the addition of thiols to (**1**). However, in that case, a high yield of the adduct is obtained. Fortunately, a hydrolytic work-up of the impure (2) readily leads to diphenylphosphinosuccinic acid (**3**) in a pure state. The structure of the anhydride was unambiguously assigned on the basis of the ^{1}H, ^{13}C and ^{31}P NMR spectra (see Experimental). Furthermore, the compound was identical with an authentic sample prepared by an independent route (see Scheme).



We have not observed similar undesired side reactions with the other activated olefins tested by us. Methylmaleic anhydride (**4**) reacts with diphenylphosphine at a much lower rate than the unsubstituted anhydride and the reaction must be performed at 60°C to result in any conversion. The anhydride is preferentially attacked by the phosphine at the substituted carbon atom and compounds (**5**) and (**6**) are obtained in a ratio of 5:1. A similar mode of addition was observed in the

TABLE I

Conversion as a function of the structure of the activated olefin

Activated olefin	Conversion[a] (%)	Time (h)	Temp (°C)	solvent
Maleic anhydride	>75[b]	2	20	$CDCl_3$
Methylmaleic anh.	30	60	60	$CDCl_3$
Dimethylmaleic anh.	<5	48	150	neat
Dimethyl maleate	30	20	20	$CDCl_3$
Dimethyl fumarate	<3	20	20	$CDCl_3$
Di sodium maleate	0	20	100	D_7-DMF

[a] Conversion of olefin, concentration of diphenylphosphine and olefin 0.2–0.3 mol/l.
[b] 5% in 3 h with $(4\text{-}CF_3C_6H_4)_2PH$.

reaction between thiols and methylmaleic anhydride.[8] Dimethylmaleic anhydride was found to be totally inactive even under much more drastic conditions (see Table I).

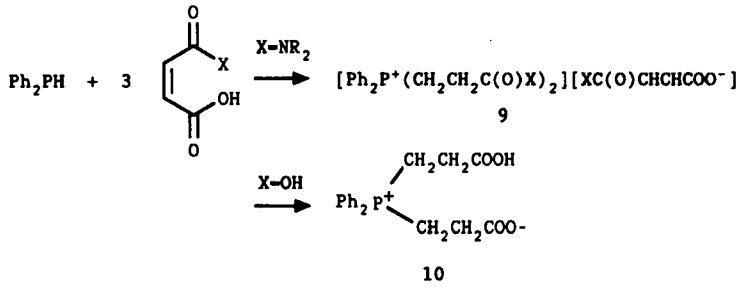
We have found that the addition reaction also occurs with acyclic structures and with various X and Y groups provided that X and Y have sufficient electron-withdrawing capacity (see Table I for a comparison of rates). For instance, the relatively electron-rich di sodium maleate, X=Y=ONa, does not react with diphenylphosphine. Diphenylphosphine adds readily to dimethyl maleate but the ester is also isomerised to dimethyl fumarate. The resultant fumarate ester proved to be less reactive than the maleate ester and, therefore, long reaction times are required for complete conversion of dimethyl maleate. After saponification, a high yield (81%) of diphenylphosphinosuccinic acid (**3**) is obtained.

We have also observed cis to trans isomerisation of cis-1,2-dicyanoethene upon reaction with diphenylphosphine, but no addition product was obtained in this case.

Unexpectedly, compounds with a carboxylate moiety, such as maleamic acids (X=OH, $Y=NR_2$) or maleic acid (X=Y=OH) react in an entirely different manner. According to ^{31}P NMR, the secondary phosphine reacts with three equivalents of the olefinic compound, with phosphonium salts being formed as the eventual products. The cationic part of the salt contains two fragments that are derived from the maleamic acid and the anion is formed from the third equivalent of the acid. We have monitored the reaction of *N,N*-dibenzylmaleamic acid and diphenylphosphine in $CDCl_3$ at 20°C by ^{31}P NMR. The spectra show that the expected product, diphenylphosphinosuccinamic acid, may be present ($\delta = -1.5$) although at a low concentration. In addition, a small amount of another product ($\delta = -16.2$), which was tentatively identified as *N,N*-dibenzyl, 3-diphenylphosphinopropionic amide, is obtained. Both compounds are converted to the eventual phosphonium salt (**9**) as the reaction proceeds.

Maleic acid probably gives initially a similar product, which on prolonged reflux in THF, is converted to the crystalline betaine (**10**).

The structures of the phosphonium salts were assigned on the basis of the characteristic ^1H, ^{13}C and ^{31}P NMR spectra and elemental analysis. Moreover, the spectra of the phosphonium salt derived from *N,N*-dibenzylmaleamic acid are almost identical with those of the analogous salt with chloride as the counter ion.



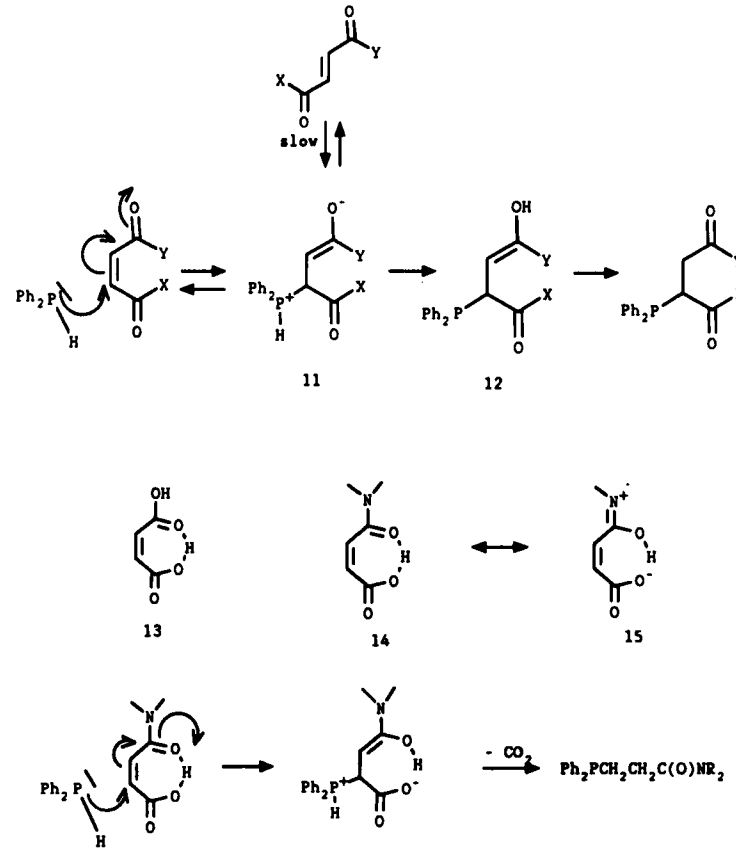
The anhydride ring can be opened by the addition of water and sodium hydroxide. The corresponding succinic acid derivative is obtained by acidification of the water layer. The phosphinosuccinic acid decarboxylates readily at elevated temperatures to form diphenylphosphinopropionic acid, and this sequence of reactions offers an attractive synthesis route for this compound.

DISCUSSION

The reaction between diphenylphosphine and methylmaleic anhydride occurs predominantly at the olefinic carbon atom that bears the methyl group. This mode of addition is not compatible with a radical mechanism[9] and it suggests that the addition of the phosphine proceeds via the well-known Michael addition mechanism. The sterically unfavourable attack at the most hindered olefinic carbon atom leads to a more stable intermediary carbanion than attack at the unsubstituted olefinic carbon atom. The cis to trans isomerisation of both maleic ester and cis 1,2-dicyanoethene in the presence of diphenylphosphine shows that the initial reaction of the secondary phosphine with the activated olefin is reversible. A similar, reversible reaction has been observed in the reaction of $R_2P^{\cdot}$ to olefins.[10] Apparently, a reaction occurs with cis-dicyanoethene but no adduct is eventually obtained from this compound. This strongly suggests that the transfer of the proton from the positively charged phosphorus atom in the zwitterion intermediate (**11**) is a crucial step. It would seem that this transfer to either a nitrogen or a carbon atom is slow or does not occur, whereas the transfer to a strongly negatively charged oxygen atom, to form (**12**), is relatively fast.

The formation of phosphonium salts from olefins with a carboxylate group (maleic acid and maleamic acids) is a hindrance from a synthetic point of view. However, the mechanism by which it is formed is interesting. Extensive intermolecular hydrogen bonding occurs in carboxylic acids and this leads to the formation of dimers or higher aggregates.[11] Due to the particular structural features of maleic and maleamic acids, intramolecular hydrogen bonding will occur. In other words, the proton of the carboxylate moiety is partially bound to the carbonyl oxygen atom of the other moiety and this leads to structures (**13**), (**14**) and (**15**).

When a secondary phosphine reacts with the molecule at the olefinic carbon atom, a negative charge develops at the carbonyl oxygen atom and this will



increase the bonding strength of the bridging proton with this oxygen atom. As a result, the expected zwitterion (**11**) is not obtained and the proton shift that occurs from the carboxylic acid moiety to the carbonyl oxygen atom impedes the essential shift of the proton from the phosphorus atom to the carbonyl oxygen atom. Clearly, a proton shift from the positively charged phosphorus atom to the negatively charged, adjacent carboxylate moiety would still lead to the expected addition product. However, the zwitterions with this structure are very prone to decarboxylation.[12] Loss of carbon dioxide leads to a tertiary phosphine which is a better donor than diphenylphosphine. As expected,[13] reaction of this phosphine with two equivalents of maleic or maleamic acid leads to the formation of phosphonium salts.

CONCLUSION

Secondary phosphines add to activated olefins such as maleic anhydride and dibenzoylethene to form the expected Michael addition product. The reaction

with maleic anhydride is complicated by secondary reactions of this anhydride. Olefins with a carboxylate group lead to the formation of phosphonium salts. It appears that a proton shift in an intermediary zwitterion determines which product will be formed. A proton shift from the phosphorus atom to a negatively charged oxygen atom leads to the expected adduct, whereas a proton shift from a carboxylic acid moiety eventually leads to the formation of phosphonium salts.

EXPERIMENTAL

Manipulations with phosphines were performed in an argon atmosphere using Schlenk techniques or under nitrogen in a glove box. Solvents were dried with sodium wire or with molecular sieves. Compounds which are not mentioned in the Experimental section were obtained commercially or were prepared by well established methods. The NMR spectra were recorded with Bruker 90, 250 and 400 MHz spectrometers. The data are presented together with the experimental procedures. Coupling constants with phosphorus are given in parentheses and CH coupling constants are given in square brackets. Chemical shifts are reported in ppm. The hydrogen atoms are numbered as follows: PCH_1, H_1 cis or syn to H_2, H_3 cis or syn to P. A number of compounds were converted to the corresponding oxide or sulfide by reaction with t-butyl hydroperoxide or elemental sulfur, respectively. The compounds were not isolated; the NMR data support the proposed structure.

NMR data of diphenylsuccinic anhydride (**2**). A solution of 9.8 g (0.1 mol) of maleic anhydride in 150 ml of THF is added over ca. 2 h to a stirred solution of 17.4 ml (0.1 ml) of diphenylphosphine in 50 ml of THF. Gradually, some solid is deposited and the orange solution is left overnight. The solvent is removed in vacuo, leaving an oil that contains compound (2) at a yield of ca. 50%. An attempt to purify the anhydride by vacuum destillation was unsuccessful. A vivid decomposition occurs and a viscous black mass is formed.
NMR ($CDCl_3$): ^{31}P, +1.9; ^1H, H_1 3.83, H_2 2.74, H_3 3.14, JH_1H_2 4.5, JH_1H_3 10, JH_2H_3 19, JPH_1 4.5, JPH_2 11, JPH_3 9; ^{13}C, CHP 38.5 (29) [141], CH_2 32.4 (14) [138], CO 170.8 (6) and 169.3 (3), i 132.97 (6) and 132.72 (6), o 132.93 (21) and 132.88 (20), m 128.73 (7) and 128.69 (7), p 129.8.

Diphenylphosphinosuccinic acid (**3**). (a) *from bromosuccinic acid.* Triphenylphosphine (92 g, 0.35 mol) is added in portions to a solution of 16.2 g (0.7 mol) of sodium in ca. 1 l of liquid ammonia at −78°C. The mixture is stirred until the colour changes from blue to orange. After 15 minutes 34.7 g (0.18 mol) of bromosuccinic acid is added to this solution. (Due to the excess of base the acid is converted *in situ* to the sodium salt). The mixture is stirred for 2 h at −78°C, then the cooling bath is removed and the ammonia is allowed to evaporate overnight. The white residue is dissolved in an aqueous NaOH solution and neutrals are removed by extraction with diethyl ether. The aqueous layer is separated and acidified with 10% HCl acid with ice cooling until the pH reaches 2. An oil separates, which crystallises readily. The white crystals are collected by filtration, washed with water and dried in a vacuum dessicator over P_2O_5. Yield 21.4 g (0.07 mol, 39%) of the pure title compound.

(b) *from maleic anhydride.* A solution of 9.8 g (0.1 mol) of maleic anhydride in 150 ml of THF is added over ca. 1 h to a stirred solution of 26.1 ml (0.15 mol) of diphenylphosphine in 50 ml of THF. The solution becomes orange and is left overnight at room temperature. Subsequently, 50 ml of water is added, the mixture is stirred for ca. 1 h and then most of the THF is removed in vacuo. To the residue a solution of 12 g NaOH in 250 ml water and 200 ml of ethyl acetate are added. The aqueous layer is separated and acidified with HCl. An oil separates that crystallises overnight. The slightly pink crystals were collected by filtration, washed with water and, subsequently, dried in vacuo. Yield 21.3 g (70.5 mmol, 70.5%) Elemental analysis: $C_{16}H_{15}O_4P$ requires: C 63.58, H 5.00, P 10.25, O 21.2%; found C 63.44, H 5.12, P 10.13, rest 21.4%.
NMR (CD_3OD): ^{31}P, 2.93; ^1H, H_1 3.74; H_2 2.38, H_3 2.77, JH_1H_2 3.5, JH_1H_3 11.5, JH_2H_3 17, JPH_1 2, JPH_2 6.5, JPH_3 5.5.
NMR oxide (CD_3OD): ^{31}P 37.0; ^1H, H_1 4.17, H_2 2.52, H_3 3.04, JH_1H_2 3, JH_1H_3 11.5, JH_2H_3 17.5, JPH_1 14.5, JPH_2 9, JPH_3 5.5; ^{13}C (D_6-DMSO) CHP 43.9 (58) [128], CH_2 30.9 [120], CO 172.1 (16.5) and 169.4 (4).
NMR sulfide (CD_3OD): ^{31}P, 49.6; ^1H, H_1 4.43, H_2 2.40, H_3 3.05, JH_1H_2 3, JH_1H_3 11.5, JH_2H_3 17.5, JPH_1 14, JPH_2 10, JPH_3 6.

(c) *from dimethyl maleate.* A solution of 16.0 g (111.1 mmol) of dimethyl maleate and 15 ml (86.2 mmol) of diphenylphosphine in 50 ml of chlorobenzene is heated in an oil bath at ca. 130°C for

ca. 60 h. Subsequently the solvent is removed in vacuo and the residue is saponified with NaOH/water/ethanol. Work-up as above gives 21.1 g (69.9 mmol, 81%) of white crystals.
NMR of the ester (**7**): ^{1}H, H_1 3.9, H_2 2.56, H_3 3.09, JH_1H_2 4, JH_1H_3 11, JH_2H_3 17.5, JPH_2 6.5, JPH_3 6.5.

(d) *from maleic acid.* A mixture of 5.5 g (47.4 mmol) of maleic acid 8.3 ml (47.7 mmol) of diphenylphosphine in 200 ml of chloroform is stirred overnight. A large amount of a white precipitate is formed. Work-up as above gives ca. 1 g (3.3 mmol, 7%) of diphenylphosphinosuccinic acid. The phosphonium salts remain in the water layer.

1,2-dibenzoyl, 1-diphenylphosphinoethane (**8**). To a solution of 2.275 g (9.64 mmol) of trans 1,2-dibenzoylethene in 25 ml of THF 1.7 ml (9.77 mmol) of diphenylphosphine is added from a syringe. The mixture is left overnight at room temperature, the solvent is removed in vacuo and diethyl ether is added to induce crystallisation. The crystals are collected by filtration, extensively washed with cyclohexane and dried in vacuo (12 mm Hg). Yield 3.667 g (8.69 mmol, 90%) of pale yellow crystals.
Elemental analysis: $C_{28}H_{23}O_2P$ requires: C 79.62, H 5.45, P 7.33, O 7.60%; found C 79.18, H 5.61, P 7.31, rest 7.9%.
NMR ($CDCl_3$): ^{31}P −0.9; ^{1}H, H_1 5.17, H_2 3.23, H_3 4.09, JH_1H_2 2.5, JH_1H_3 11, JH_2H_3 18.5, JPH_1 2.5, JPH_2 6, JPH_3 3.5.
NMR oxide (D6-DMSO): ^{13}C CHP 44.9 (57) [132], CH_2 37.5 [129], CO 196.4 (14) and 196.2 (4).

3-(diphenyl,2-carboxyethylphosphonio)propionate (**10**). To a solution of 2.0 g (17.2 mmol) of maleic acid in 50 ml of THF 3.0 ml (17.3 mmol) of diphenylphosphine is added. The mixture is kept overnight in an oil bath at 60°C. An oil is deposited, which is slowly converted to white crystals on prolonged refluxing (ca. 30 h). The crystals are filtered off and dried in vacuo. Yield 1.1 g, 58% for a stoichiometry of 1:3 (see text).
Elemental analysis: $C_{18}H_{19}O_4P$ requires C 65.45, H 5.80, p 9.38%; found C 65.30, H 5.89, P 9.48%.
NMR (CD_3OD): ^{31}P 30.0; ^{1}H PCH_2 3.48 (13), CH_2CO 2.73 (13); ^{13}C PCH_2 18.5 (52.7) [135], CH_2CO 28.7 (3.1) [129], CO 175.2 (13.9) i 119.5 (84.1), o 134.2 (9.4) [165], m 131.3 (12.4) [166], p 136.0 (2.9) [165].

Bis-(N,N-dibenzyl-2-carboxamidoethyl), diphenylphosphonium chloride. *N,N*-dibenzyl-3-diphenylphosphinopropionamide is prepared by reaction of sodium diphenylphosphide and *N,N*-dibenzyl-3-chloropropionamide in liquid ammonia/THF. NMR ($CDCl_3$): ^{31}P −16.1; ^{1}H CH_2CH_2 2.5, CH_2N 4.57 and 4.29.

An equimolar mixture of *N,N*-dibenzyl-3-diphenylphosphinopropionamide and *N,N*-dibenzyl-3-chloropropionamide is slowly heated to 180°C and kept at this temperature for 5 h. The product is cooled and crushed in a mortar. The yield is quantitative.
Elemental analysis: $C_{46}H_{46}ClN_2O_2P$ requires C 76.18, H 6.39, Cl 4.89, N 3.86, P 4.27; found C 76.04, H 6.43, Cl 5.00, N 3.80, P 4.14.
NMR ($CDCl_3$): ^{31}P 30.0; ^{1}H CH_2P 3.66 (12), CH_2CO 2.96 (18), CH_2N 4.46 and 4.37; ^{13}C CH_2P 18.4 (55), CH_2CO 26.8 (3), CO 170.0 (8.3), CH_2N 49.8 and 48.8, PPh, i 119.0 (84), o 132.9 (9), m 129.4 (12), p 133.7 (3), NCH_2Ph i 136.2 and 135.6, o 127.7 and 127.1, m 128.5 and 128.2, p 126.1.

3-diphenylphosphinopropionic acid. A mixture of 20.7 g (68.5 mmol) of diphenylphosphinosuccinic acid and 10 ml of toluene is heated in an oil bath at 130°C for three hours. The initially solid mass gradually changes into an oil. After cooling to room temperature, 100 ml of a 5% NaOH solution is added to dissolve the product. The aqueous layer is extracted with ethyl acetate and, subsequently, acidified with 10 ml of concentrated HCl. An oil separates, which crystallises overnight. The crystals are collected by filtration, thoroughly washed with water and dried in vacuo. Yield 15.8 g (61.2 mmol, 89.3%) of pure compound which is identical to an authentic sample.

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