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TRITYLONE ETHERS*

CLEAVAGE, STABILITY AND SELECTIVITY OF FORMATION

W. E. BARNETT, L. L. NEEDHAM† and R. W. POWELL‡
Department of Chemistry, University of Georgia, Athens, Georgia 30601

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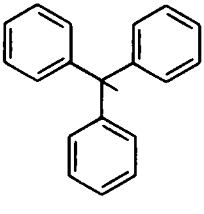
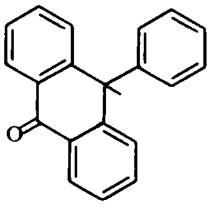
Abstract—Alcohols react readily with 9-phenyl-9-hydroxyanthrone to form substituted trityl ethers which are more stable to acid than traditional trityl ethers. These new tritylone ethers enjoy an additional advantage over trityl ethers in that they can be readily cleaved by a specific base-catalyzed reaction, the Wolff–Kishner reduction. The tritylone ether-forming reaction is selective for primary alcohols in the presence of secondary alcohols.

TRITYL ethers are stable to a wide variety of non-acidic reagents but are easily hydrolyzed by dilute acid.[1] Because of these properties, the trityl group I is one of the most important protecting groups for OH-containing functions. This is especially true for carbohydrates where the trityl group, because of its bulkiness, may be selectively attached to one of several OH functions and may also enhance the solubility of the carbohydrate in organic solvents.[2] We have been trying to devise a protecting group which would retain many of the advantages of the trityl group but which would exhibit an increased stability to acidic conditions and more selectivity toward methods of removal, especially removal by a reaction carried out under basic conditions. The tritylone group, II, is such a group; it is readily removed by base-catalyzed Wolff–Kishner reduction[3] and it is more stable to acid hydrolysis than trityl.



I



II

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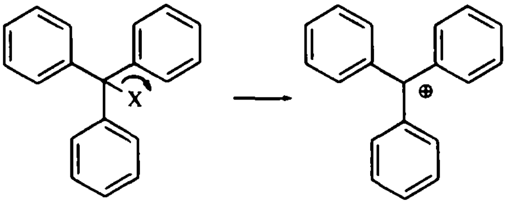
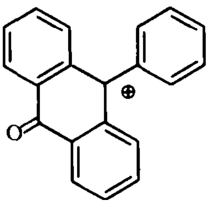
Presumably the very stable nature of the trityl cation, III, is a factor determining the acid lability of trityl protecting groups.[2]* It seemed that substitution which could destabilize the trityl cation might afford a trityl derivative more stable to acid-catalyzed hydrolysis.† If for example a CO group were attached to the trityl moiety so that the electrophilic CO carbon atom could interact with the developing positive charge of the cation, the bond-breaking process IV → III might be less favorable. Several sites of attachment are possible. Our efforts have been directed toward development of the group II, related to cation V. Of the possible monocarbonyl systems, this protecting group has several advantages with regard to its removal.

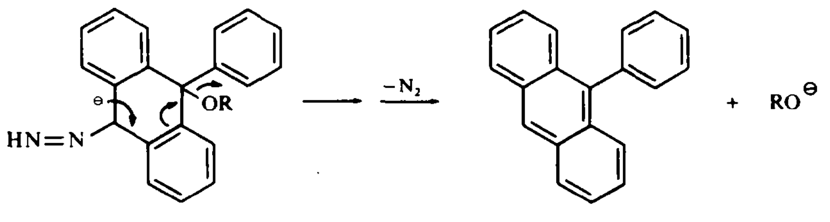


IV III



V

It was envisioned that a suitably substituted carbonyltrityl protecting group could be removed by Wolff–Kishner reduction since the accepted mechanism of that reaction[6] involves the conversion of the electrophilic CO carbon atom into a carbanionic center during the reaction. Thus during Wolff–Kishner reductions, α-halo ketones and other ketones having leaving groups on the α C atom undergo elimination[7] *via* such carbanionic intermediates. It was expected that placing a phenyl ring between the CO carbon and the carbon bearing the leaving group would make no great difference and that elimination would still predominate. However, of the monocarbonyl systems considered, only the system II would lead to a stable by-product. 9-phenylanthracene, VI → VII.



VI VII

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* Structural limitations in the linear relation between cation stabilities and their reactivities have been shown for a limited variety of trityl derivatives having strongly electron-donating substituents. the conclusion being that arguments regarding cation stability based upon solvolysis rates should be regarded as tenuous; see ref. 4. It is difficult to make a fair assessment of these results since the dialkylamino compounds reported are anomalous in other ways; see discussion above Table II in ref. 5. At any rate, no work has been done on trityl derivatives having electron-withdrawing functionality

† For diphenylchloromethane derivatives, rates of solvolysis have been related to free energies of ionization. Thus an electron-withdrawing 4-chloro substituent produces a less stable cation than the diphenylmethyl cation and a more slowly solvolyzing substrate than diphenylchloromethane; see Table V. ref. 5.

In practice, the Wolff–Kishner method is an efficient one for cleaving tritylone ethers. NMR examinations of crude reaction mixtures show quantitative conversions of trityl ethers to the respective alcohols. In the case of water-insoluble alcohols a very high yield of recovered alcohol can be obtained as evidenced by the recovery of an 88% yield of pure hexadecanol from hexadecanyl tritylone ether. Only one case of a water-soluble alcohol has been done, 1,4-butanediol being recovered in 50% yield. However, we do not expect this low recovery to be general for water-soluble alcohols. Higher molecular weight polyols should not share the difficulties associated with the isolation of this low molecular weight diol. Alcohols are separated from the by-product 9-phenylanthracene by crystallization, chromatography or extraction with water.

In order to assess the relative stabilities of the trityl and tritylone groups in acidic media, a rough comparison of the rates of hydrolysis was made. Experiments with the trityl and tritylone ethers of hexadecanol indicate that the latter is much more stable to acidic conditions, as we suspected it might be. Thus 0·40 mmole of each compound was dissolved in 6 ml of THF and 1·5 ml of 10% HCl was added so that each mixture was slightly cloudy; these were stirred 18 hr at 30–31°. NMR analysis showed that the trityl ether was approximately 50% hydrolyzed while the tritylone ether was essentially intact. A similar reaction for 54 hr showed very little tritylone hydrolysis and almost complete trityl cleavage. This demonstrated that the tritylone group exhibited the increased stability to acid we were searching for.

Only a few simple 9-alkoxy-9-phenylanthrones have been reported previously in the literature and methods for synthesizing them require reacting a tritylone derivative with a large excess of alcohol. Ethyl tritylone ether[8] has been prepared from tritylone chloride[9] and excess refluxing ethanol. Butyl tritylone ether has been prepared from the methyl ether by acid-catalyzed exchange in refluxing butanol,[10] and the acid-catalyzed reaction of tritylone alcohol in aqueous acidic ethanol affords a reasonable yield of the ethyl ether as described.[11] For the tritylone group to be generally useful, however, a method for preparing ethers from equimolar amounts of alcohol and tritylone derivative was desirable. The aforementioned procedures cannot be so used and thus new methods for attaching the tritylone group were explored. Reaction of tritylone chloride with one equivalent of ethanol and one equivalent of triethylamine did not lead to any significant amount of ether; substitution of pyridine as the solvent produced no change. Reaction of tritylone chloride in the presence of silver nitrate produced only a low yield of ether. Apparently, the tritylone cation is sufficiently destabilized so that there is no reaction analogous to the synthesis of trityl ethers from trityl chloride.

Having thus failed in our initial attempts to use the chloride, we began to study tritylone alcohol. A convenient method of tritylone ether formation was soon developed. One equivalent of tritylone alcohol and one equivalent of the alcohol to be protected are refluxed in benzene containing a trace of *p*-toluenesulfonic acid; water is removed as the benzene azeotrope. This method works reasonably well for secondary alcohols and quite well for primary alcohols. Tertiary alcohols react slowly if at all; in certain cases they may be dehydrated under these conditions. The tritylone ethers shown in Table 1 have been prepared.

In dealing with polyhydroxylated compounds there are instances where one of the several OH functions should be selectively protected. Trityl ether formation has been shown[1] to be selective for unhindered alcohols in such situations. We wondered if a similar selectivity might be displayed in the acid-catalyzed formation of tritylone ethers. Although the tritylone is as bulky as the trityl group, it was not at all certain what effect the destabilized cation intermediate would have on the competition for primary and secondary OH groups. In spite of the considerable differences in the trityl and tritylone cations, we have found that the tritylone group exhibits a marked selectivity, much like that of the trityl group. This is shown by two experiments. In the first, equimolar amounts of tritylone alcohol, 1-octanol and 2-octanol reacted leading to exclusive formation of the 1-octanyl ether in high yield. In the second experiment 1.3-butanediol was subjected to ether formation using one equivalent of tritylone alcohol. As evidenced by NMR of the crude mixture, reaction occurred only at the primary alcohol group. The hydroxy ether could be isolated in excellent yield.

TABLE 1

ROH	Yield of tritylone ether	m.p. of ether
Hexadecanol	88%	63–64°
Dodecanol	86%	53–54°
1-Octanol	95%	44–45°
2-Octanol	75%	44–45°
Cholesterol	59%	204–206°
Cyclohexanol	55%	170–171°
Butane-1.-diol	79%	117·5–119·5°

Tritylone alcohol can be synthesized by chromic acid oxidation of 9-phenylanthracene as described in the literature for methoxy-9-phenylanthracenes.[12] Moderate quantities of 9-phenylanthracene can be readily prepared by dehydration of the reaction product from anthrone and phenylmagnesium bromide.[13] Also 9-phenylanthracene produced from the Wolff–Kishner reduction of tritylone ethers can be recycled to give tritylone alcohol.

EXPERIMENTAL

The NMR spectra were taken in $CDCl_3$ soln with a Varian HA-100 NMR spectrometer. M.ps were taken on a Thomas-Hoover capillary tube m.p. apparatus and are uncorrected. All IR spectra were taken in $CHCl_3$ soln on a Perkin-Elmer Model 257 infrared spectrometer. They were calibrated at 1603 cm^{-1} with a polystyrene film.

9-Phenylanthracene[13] was prepared in 41% yield by the method of Norman and Waters: pale yellow crystals; m.p. 149–151°; (Lit.[13] m.p. 156°).

9-Hydroxy-9-phenylanthrone[12] (Tritylone alcohol) was obtained by the oxidation of 9-phenylanthracene: 73% yield, recrystallized from EtOAc–hexane, m.p. 213–214°; (Lit.[9] m.p. 211–212°).

Tritylone hexadecanyl ether. To 4·107 g (14·36 mmoles) of 9-hydroxy-9-phenyl anthrone in a 125 ml r.b. flask was added 3·475 g (14·36 mmoles) of hexadecanol, 0·1365 g (0·72 mmole) of *p*-toluenesulfonic acid, and 25 ml of dry benzene. The flask was then fitted with a Dean–Stark trap (which was filled with dry benzene). To the trap was attached a water-cooled reflux condenser which was fitted with a $CaCl_2$ drying tube. The reaction mixture was allowed to reflux for 11 hr (bath temp, 115°); the solvent was evaporated. The dark residue was dissolved in CH_2Cl_2 (1·5 ml) and pre-adsorbed on neutral alumina. Chromatography gave the tritylone ether from the 1:9, ether:light petroleum fractions, yield: 6·45 g (88%); m.p. 63–64°. (Found: C, 84·53; H, 9·10. Calc. for $C_{36}H_{42}O_2$: C, 84·65; H, 9·07%); NMR: τ 1·60–1·66 mult (2 H), 2·49–2·87 mult (11 H), 7·0 trip (2 H), 8·72 sing (27 H), and 9·1 mult (3 H). The 2 protons at 7·0 τ were apparently due to the —OCH_2-group; in hexadecanol, the —OCH_2-triplet was at 6·4 τ. IR: cm^{-1} 1667 (C=O) and 1602

Tritylone 1-octanyl ether. A procedure similar to the one described for the preparation of tritylone hexadecanyl ether was used. However, the mixture was heated to reflux (bath. 116°) for 19 hr. Chromatography resulted in a 95% yield of the tritylone ether (1:6, ether:light petroleum); m.p. 44·5–45°. (Found: C, 84·34; H, 7·69. Calc. for $C_{28}H_{30}O_2$: C, 84·37; H, 7·69%); NMR: τ 1·8 mult (2 H), 2·67–3·05 mult (11 H), 7·0 trip (2 H), and 8·6–9·2 mult (approx 15 H).

Tritylone cholesteryl ether. A procedure similar to the one described for the preparation of tritylone hexadecanyl ether was used. However, the mixture was heated to reflux (bath. 110°) for 20 hr. Chromatography resulted in a 59% yield of the tritylone ether (1:9, ether:light petroleum): m.p. 204–206·5°. (Found: C, 86·03; H, 9·13. Calc. for $C_{45}H_{58}O_2$: C, 86·19; H, 8·92%); NMR: τ 1·7 mult (2 H), 2·58–2·88 mult (approx 11 H), 5·18 mult (2 H), 6·94 mult (1 H), and 8·02–9·39 mult (35 H); IR: cm^{-1} 1667 (C═O), 1607.

Tritylone cyclohexanyl ether. A procedure similar to the one described for the preparation of tritylone hexadecanyl ether was used. However, the mixture was heated to reflux (bath. 116°) for 16 hr. Chromatography resulted in a 55% yield of the tritylone ether (1:8·5, ether:light petroleum); m.p. 170–171°. (Found: C, 84·63; H, 6·73. Calc. for $C_{26}H_{24}O_2$: C, 84·75; H, 6·57%); NMR: τ 1·57–1·67 mult (2 H), 2·53–2·82 mult (11 H), 6·74 mult (1 H), and 8·56–9·26 mult (approx 10 H). IR: cm^{-1} 1657 (C═O); 1602.

Tritylone 2-octanyl ether. A procedure similar to the one described for the preparation of tritylone hexadecanyl ether was used. However, the mixture was heated to reflux (bath, 115°) for 16 hr. Chromatography resulted in a 75·5% yield of the tritylone ether (1:9, ether:light petroleum); m.p. 44–45°. (Found: C, 84·37; H, 7·70. Calc. for $C_{28}H_{30}O_2$: C, 84·38: H, 7·59%); NMR τ 1·63–1·71 mult (2 H), 2·63–2·93 mult (11 H), 6·60 mult (1 H), and 8·85–9·18 mult (16 H); IR: cm^{-1} 1667 (C═O); 1602.

Tritylone dodecyl ether. A procedure similar to the one described for the preparation of tritylone hexadecanyl ether was used. However, the mixture was heated to reflux (bath, 116°) for 10 hr. Chromatography resulted in an 86% yield of the tritylone ether (1:9, ether: light petroleum); m.p. 53–54°. (Found: C. 84·32; H, 8·27. Calc. for $C_{32}H_{38}O_2$: C, 84·54; H, 8·42%); NMR: τ 1·64 mult (2 H), 2·58–2·96 mult (approx 11 H), 7·0 trip (2 H), 8·74 sing (20 H). and 9·14 mult (3 H); IR: cm^{-1} 1662 (C═O), 1602.

Huang-Minlon reduction.[3] To 1·89 g (3·7 mmole) of tritylone hexadecanyl ether in 30 ml triethylene glycol was added 0·44 g (11·1 mmoles) of NaOH. The temp of the mixture was raised to 80° to facilitate dissolving the NaOH and the tritylone ether. Then 0·5 cc 95% + hydrazine was added. The temp was kept at approximately 125° for 1½ hr. The temp was then raised to 195° and held there for 4 hr. The mixture was allowed to cool to room temp and the soln was acidified (15 ml of 5% HCl), extracted with benzene, and washed twice with H_2O (50 ml). The H_2O layer was extracted once again with benzene and this organic layer was washed twice with 50 ml H_2O. The organic solns were combined and dried overnight (Na_2SO_4). After filtration, the solvent was evaporated yielding 1·76 g dark solid. The alcohol was purified *via* column chromatography on alumina using light petroleum–ether mixtures. A good yield of 9-phenylanthracene was obtained from the early fractions. The hexadecanol was eluted with 100% ether in a near-quantitative yield. The product was identical with an authentic sample of hexadecanol.

Heterogeneous hydrolysis with THF co-solvent. To 0·2320 g tritylone hexadecanyl ether in 6 ml THF was added 2·4 ml 10% HCl. Then an additional 1·5 ml THF was added. The hexadecanyl trityl ether was treated in the same way. Each mixture was a 2-phase system.

The solns were stirred magnetically for 12 hr at room temp. To each soln 100 mg $NaHCO_3$ and 25 ml THF was added. The layers were separated; the THF layer was dried (Na_2SO_4), filtered, and evaporated. NMR analyses of the residues showed that the trityl ether had slightly hydrolyzed while the tritylone ether had hydrolyzed to an even lesser degree. To each of the residues was added 2·4 ml 10% of HCl and 7·5 ml THF. The solns were then stirred for an additional 54 hr and were worked up as before. NMR analyses showed the trityl compound had largely hydrolyzed while the tritylone ether had hydrolyzed only to a small degree.

Tritylone ethyl ether.[11] The procedure of Awad, *et al.* was modified as follows: To 0·3041 g (1·06 mmoles) 9-hydroxy-9-phenylanthrone was added 3·75 ml conc HCl and 3·75 ml EtOH. The mixture was refluxed for 2 hr. After cooling, 50 ml ether was added. The organic layer was then washed twice with 10 ml H_2O. The layers were again separated and dried ($MgSO_4$), filtered, and concentrated. The crude yield was 0·3382 g. This material was recrystallized from light petroleum, yield 0·1810 g; m.p. 157·5–158° (Lit.[11] 159–160°).

Tritylone 1-butoxy-3′-ol ether. A procedure similar to the one described for the preparation of tritylone hexadecanyl ether was used. Chromatography (1:1, MeOH: light petroleum) yielded 0·7902 g (79%); NMR: τ 1·66–1·74 mult (2 H), 2·30–2·98 mult (11 H), 5·88–6·07 mult (1 H), 6·73–6·86 trip (2 H), 7·20 mult (1 H), 8·20–8·30 mult (2 H), and 8·83–8·89 doub (3 H). For analysis, the product was recrystallized from light petroleum/ether. m.p. 117·5–119·5°. (Found: C, 80·14; H, 6·25. Calc. for $C_{24}H_{22}O_3$; C, 80·42; H, 6·25%); IR (CCl_4): cm^{-1} 3562 (OH); 1667 (C=O).

A competitive reaction between 1-*octanol and* 2-*octanol.* To 0·900 g (2·83 mmoles) 9-hydroxy-9-phenylanthrone was added 0·3682 g (2·83 mmoles) 1-octanol and the same amount of 2-octanol. Then 0·0266 g (0·14 mmoles) *p*-toluenesulfonic acid and 25 ml benzene were added and the mixture was refluxed for 48 hr. The mixture was worked up in the usual manner, yield: 1·0599 g. NMR analysis of the residue indicated that the tritylone 1-octanyl ether was formed in greater than 90% yield whereas the 2-octanol ether could not be detected.

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