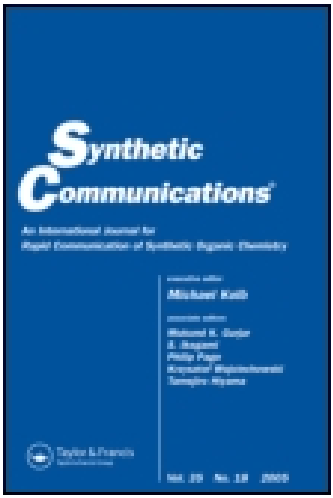

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Easy Large Scale Syntheses of 2,6-DI-t-Butyl- 7-Cyano-, 7-Carboxy-and 7-Methoxycarbonyl Quinone Methides

Peter Nesvadba [a]

[a] Ciba Specialty Chemicals Inc. , CH-4002, Basel, Switzerland E-mail:

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EASY LARGE SCALE SYNTHESES OF 2,6-DI-*t*-BUTYL-7-CYANO-, 7-CARBOXY- *AND* 7-METHOXYCARBONYL QUINONE METHIDES

Peter Nesvadba

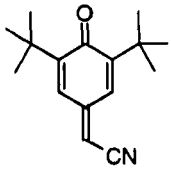
Ciba Specialty Chemicals Inc.
CH-4002 Basel, Switzerland
e-mail: peter.nesvadba@cibasc.com

Abstract: Easy large scale syntheses of 2,6-di-*t*-butyl-7-cyano-, 7-carboxy- and 7-methoxycarbonyl quinone methides **1-3** using cheap and readily available starting materials have been developed.

Quinone methides[1] being highly reactive compounds are useful as synthetic intermediates,[2] play important role in biochemical reactions[3] and have also industrial importance, for instance, as polymerization inhibitors[4] or transformation products[5] of phenolic antioxidants. Several syntheses of quinone methides are known, for example: a) oxidation of phenols with alkaline ferricyanide,[6] manganese dioxide,[7] silver oxide,[8] or lead dioxide,[9] b) base promoted elimination[10] of sulphinic acids from 4-hydroxybenzyl sulphones, c) dehydrohalogenation[11] of 4-hydroxybenzyl chlorides (or bromides), d) condensation[12] of dicarbonyl compounds with N-phenyltriazolinedione-dienone ylides derived from phenols, e) reaction of phosphonium ylides with *o*-benzoquinones. Because the cited met-

hods use relatively toxic or expensive starting materials they are not well suited to large scale preparations.

We needed an easy access to kilogram quantities of quinone methides **1-3**



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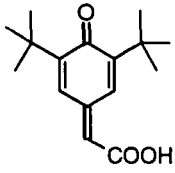

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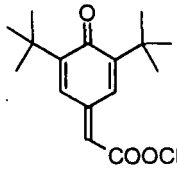
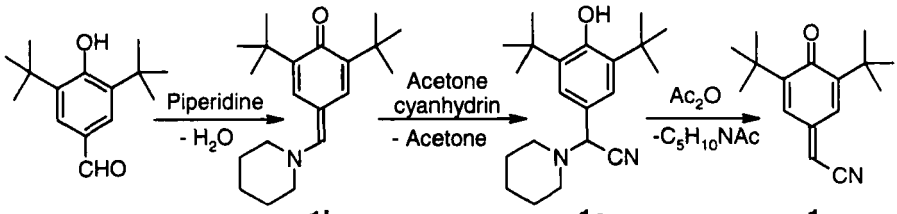


3

Unfortunately, the described syntheses[13] of **1-3** are based on the ferricyanide oxidation of the corresponding phenols which are available through multistep and rather low-yield procedures. Therefore, we have developed new, short and easily upscalable syntheses of **1-3** using readily available materials which we are reporting here.

2,6-di-*t*-butyl-7-cyano-quinone methide (**1**)

The synthesis of **1** (Scheme1) starts with the commercially[14] available 3,5-di-*t*-butyl-4-hydroxy-benzaldehyde **1a**.



1a **1b** **1c** **1**

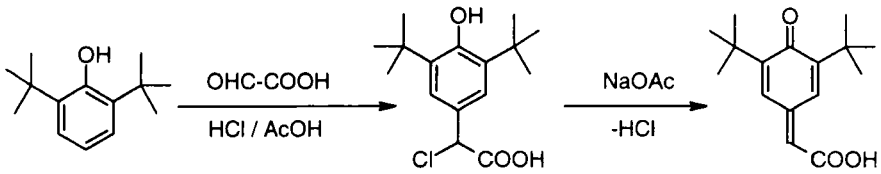
Scheme 1

Reaction of **1a** with piperidine under azeotropic removal of water with heptane affords the piperidine quinone methide **1b**. Addition of acetone cyanhydrin as an

easy to handle hydrogen cyanide source to the raw **1b** gives in a fast and quantitative reaction the aminonitrile **1c**. Treatment of the latter with acetic anhydride at reflux effects the elimination of piperidine to afford **1** in a high yield.

2,6-di-*t*-butyl-7-carboxy-quinone methide (**2**)

The very cheap 2,6-di-*t*-butyl-phenol **2a** is a starting material for **2** (Scheme 2). Its reaction with glyoxylic acid and HCl in acetic acid affords the benzylchloride[15] **2b** which on treatment with sodium acetate gives **2** through elimination of HCl.



2a **2b** **2**

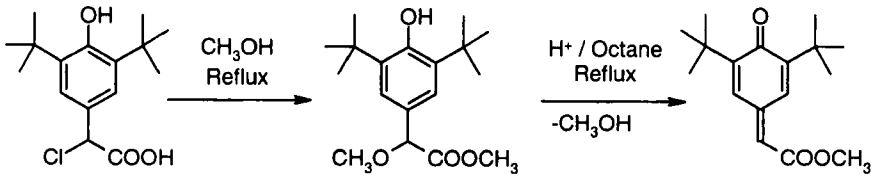
Scheme 2

2,6-di-*t*-butyl-7-methoxycarbonyl-quinone methide (**3**)

The benzylchloride **2b** represents the starting material also for **3** (Scheme 3). Refluxing of **2b** in excess of methanol gives rise to the methoxy-methylester **3a** which affords **3** through elimination of methanol during reflux in octane under acid catalysis. Solid supported acids are particularly advantageous because of the easy workup.

Experimental

The ^{1}H-NMR spectra were recorded at 300 MHz in $CDCl_3$ with TMS as an



2b **3a** **3**

Scheme 3

internal standards. The melting points are not corrected. The solvents and reagents were of a p.a. grade.

2,6-di-*t*-butyl-7-cyano-quinone methide (**1**)

A) The solution of 48.6 g (0.2 mol) of 3,5-di-*tert*-butyl-4-hydroxy-benzaldehyde hemihydrate in 150 ml heptane is dehydrated by refluxing for about 30 minutes in the Dean-Stark trap. The mixture is then cooled to 80 °C, 21.7 ml (0.22 mol) piperidine are added and the reflux in the Dean-Stark trap is continued untill the water separation stops (about 1h). The deep yellow solution is cooled to 80 °C and 21 ml (0.23 mol) of aceton cyanhydrin are added dropwise over a period of 10 minutes. The mixture is then stirred at 80 °C for another hour and evaporated on the rotary evaporator. The oily residue is dissolved in 200 ml ethanol and 30 ml water and cooled under stirring to 0 °C . The crystals are filtered off, washed with 120 ml of cold (0 °C) 80% ethanol and dried to give 55.7 g (84.8%) of the aminonitrile **1c** as a pale yellow crystals, M.p. 110-111 °C[16]. ^{1}H-NMR (δ ppm): 7.31 (s, 2H,), 5.28 (s, 1H), 4.74 (s, 1H), 2.61-2.40 (m, 4H), 1.70-1.42 (m, 6H), 1.55 (s, 2x *t*-Bu).

B) 55.7 g (0.17 mol) of **1c** are dissolved in 100 ml toluene, 19 g (0.186 mol) acetic anhydride are added and the mixture is refluxed for 1 hour. The red solution is then cooled to room temperature, washed with water, 5% sodium bicarbonate solution and water again and evaporated on the rotary evaporator. The solid residue is crystallized from 100 ml hexane to give 34.5g (83.7%) of **1** as an orange prisms, M.p. 110-111 °C.[17] ^{1}H-NMR (δ ppm): 7.33 (d, 1H, J= 4 Hz), 6.86 (d, 1H, J= 4 Hz), 5.67 (s, 1H), 1.32 (s, *t*-Bu), 1.29 (s, *t*-Bu).

2,6-di-*t*-butyl-7-carboxy-quinone methide (**2**)

A) 309.5 g (1.5 mol) 2,6-di-tert-butyl-phenol and 266.5 g (1.8 mol) 50% aqueous glyoxylic acid are dissolved in 1400 ml glacial acetic acid. 200 g (5.5 mol) of gazeous hydrogen chloride are then bubbled into the reaction mixture with stirring and cooling in an ice bath over a period of 2.5 hours, while carefully keeping the temperature between 10-25 °C. The mixture is then stirred at room temperature overnight and then cooled to 10 °C. The precipitated solid is isolated by filtration on a Buechner funnel and washed with 1000 ml water. The slightly yellow and still wet cake of the benzylchloride **2b** weighs 565 g. This material is pure enough for the next step. ^{1}H-NMR (δ ppm): 7.31 (s, 2H), 5.38 (s, 1H), 5.33 (s, 1H), 1.44 (s, 2x *t*-Bu).

B) To a cold (0 °C) solution of 24.6 g (0.3 mol) sodium acetate in 80 ml water are added 72 g of the wet benzylchloride **2b** and 50 ml toluene. The mixture is then vigorously stirred for 3 hours while the temperature rises to room

temperature. The mixture is then cooled to 0 °C again and filtered. The filter cake is washed with water and hexane and dried to give 37 g (74 %)[18] of **2** as an orange crystals, M.p. 148-150 °C. Calculated for $C_{16}H_{22}O_3$: C 73.25, H 8.45; found C 72.96, H 8.28. ^{1}H-NMR (δ ppm): 8.25 (d, 1H, J=2 Hz), 6.82 (d, 1H, J= 2 Hz), 6.18 (s, 1H), 1.32 (s, *t*-Bu), 1.31 (s, *t*-Bu).

2,6-di-*t*-butyl-7-methoxycarbonyl-quinone methide (3)

A) 117.5 g (0.393 mol) of the dry benzylchloride **2b** (prepared as described for **2** and dried at 80 °C/70 Torr), are dissolved in 250 ml methanol and the solution is heated under reflux. After 5 - 10 minutes a white solid precipitate begins to form. The suspension is refluxed for an additional 3 hours, then cooled to 0 °C and filtered. The solid is washed with 100 ml cold methanol and dried to give 109 g (89.9%) of **3a** as a white crystals, M.p. 132-133 °C. Calculated for $C_{18}H_{28}O_4$: C 70.10, H 9.15; found C 69.93, H 9.12. ^{1}H-NMR (δ ppm): 7.22 (s, 2H), 5.28 (s, 1H), 4.69 (s, 1H), 3.75 (s, CH_3O), 3.42 (s, CH_3O), 1.44 (s, 2x *t*-Bu).

B) 61.6 g (0.2 mol) of **3a** and 5.0 g of a Fulcat 22B catalyst[19] are heated in 100 ml *n*-octane under reflux in a Dean-Stark liquid separator. The evolution of methanol stops after about 1 hour. The Fulcat 22B is then filtered off from the still warm mixture and the filtrate is cooled under stirring to 0 °C. The suspension is filtered to give 43 g (78%) of **3** as an orange crystals, M.p. 87-89 °C.[20] ^{1}H-NMR (δ ppm): 8.30 (d, 1H, J=1.8 Hz), 6.78 (d, 1H, J= 1.8 Hz), 6.15 (s, 1H), 3.81 (s, CH_3O), 1.31 (s, *t*-Bu), 1.28 (s, *t*-Bu).

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