Preparation of 2-Alkyl-1,4-naphthoquinones

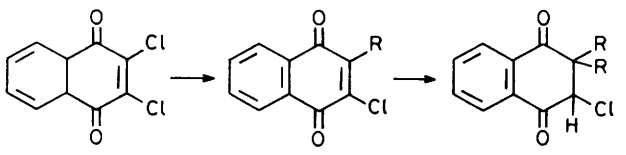
William G. Peet and Wilson Tam*

Central Research and Development Department, E. I. du Pont de Nemours and Company, Experimental Station, Wilmington, Delaware 19898, U.S.A.

The reaction of 2,3-dichloro-1,4-naphthoquinone with organo aluminium, zinc, zirconium, or tin reagents yields 2-alkyl-3-chloro-1,4-naphthoquinones; with Zr or Sn reagents, a palladium or nickel catalyst is needed.

We have discovered a convenient route to 2-alkyl-3-chloro-1,4-naphthoquinones by the reaction of the readily available 2,3-dichloro-1,4-naphthoquinone (**1**) with Al, Zn, Zr, or Sn reagents.[1] 2-Alkyl-1,4-naphthoquinones are found in nature, and several derivatives have biological activity. For example, certain 2-alkyl-3-hydroxy-1,4-naphthoquinones are antimalarials[2] and are effective against the cattle disease, East Coast Fever-Theilieria parva infection.[3] The reaction of (**1**) described in this paper constitutes a convenient route to these quinones since 2-alkyl-3-chloro-1,4-naphthoquinones can be readily converted into their hydroxy derivatives.

An 82% yield of 2-n-dodecyl-3-chloro-1,4-naphthoquinone (**2**; R = $C_{12}H_{25}$) was obtained after stirring (**1**) (20.0 mmol), $(dodecyl)_3Al$ [prepared *in situ* from $AlCl_3$ (9.4 mmol) and (dodecyl)MgBr (28.0 mmol)], and $ZnCl_2$ (40.0 mmol) in tetrahydrofuran (THF) for 10 min at room temperature. $ZnCl_2$ and magnesium salts are needed for short reaction times and good yields. Without $ZnCl_2$, a 30—45% yield of (**2**; R = $C_{12}H_{25}$) was obtained after stirring overnight. Lowering the (dodecyl)MgBr/$AlCl_3$ ratio to 2, 1.5, or 1 also decreases the yield of (**2**). Reactions of (**1**) and aluminium reagents with small alkyl groups proceed in lower yield; ethyl (40%), propyl (25%), and allyl (27%). In these cases, the monoalkylated product reacts further to give after hydrolysis the 2,2-dialkyl-3-chlorodihydronaphthoquinone (**3**)† whereas this side reaction is absent in the dodecyl case.



(**1**) (**2**) (**3**)

Similar results were obtained for alkyl zinc reagents. A stirred mixture of (dodecyl)ZnCl and (**1**) kept at room temperature overnight in THF gave 61% of (**2**; R = $C_{12}H_{25}$). Lower yields resulted with small alkyl groups; ethyl (31%), isopropyl (21%), and allyl (30%).

The reaction of (**1**) with tetra-alkyltin requires a palladium catalyst and refluxing in 1,4-dioxane. $PdCl_2$(dppp)–$HAlBu^i_2$ is a more effective catalyst than $PdCl(CH_2Ph)(PPh_3)_2$ [dppp = 1,3-bis(diphenylphosphino)propane].[4] In contrast to Al and Zn reagents, small alkyl groups lead to good yields: methyl (88%) and butyl (91%). However, the reaction is slow with a large alkyl group; a 25% yield of (**2**; R = $C_{12}H_{25}$) was obtained with tetradodecyltin after refluxing in 1,4-dioxane for 6 days. 2-Methyl-3-chloro-1,4-naphthoquinone reacted with another equivalent of $SnMe_4$ in the presence of $PdCl(CH_2Ph)(PPh_3)_2$ to yield 82% of 2,3-dimethyl-1,4-naphthoquinone. Tetra-allyltin is more reactive, one equivalent reacting with (**1**) in refluxing THF without a catalyst to give after hydrolysis a 65% yield of 2,2-diallyl-3-chlorodihydronaphthoquinone.[5]

† Satisfactory analyses and spectral data were obtained for all new compounds.

Finally, $(\eta^5\text{-}C_5H_5)_2ZrCl(alkyl)$ [prepared *in situ* from $(\eta^5\text{-}C_5H_5)_2ZrCl(H)$ and olefins in THF[6]] reacts with (**1**) in the presence of either $PdCl(CH_2Ph)(PPh_3)_2$, $PdCl_2(dppp)$, or $NiCl_2(dppp)$ catalyst to yield 2-alkyl-3-chloro-1,4-naphthoquinone: dodecyl (31—54%), octyl (39%), and cyclohexyl (31%).

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