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REACTIVITY OF NEW PRECURSORS OF QUINONE METHIDES

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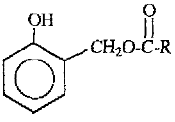
Summary : The azidomethylene protecting group allows the synthesis of unstable phenolic compounds which are used as quinone methide precursors in the alkylations of alcohols, phenols, azide, thiophenol, amines, enols and enolates.

The use of the azidomethylene group to protect the hydroxyl functional group allows the phenol to be retrieved under very mild conditions.[1] In this way, certain unstable phenols can be prepared in high yield. This is the case of phenols I and II, in particular, and of compounds of analogous structure. A few molecules of this type have been isolated and described in the literature.[2,3,4] We have noticed that many others were isolable only with great difficulty. The substances I and II (R = CH_3 ; Z = H, Cl, OCH_3), for example, can be conserved for several days in dilute solution but polymerise rapidly as soon as they are pure.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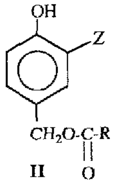
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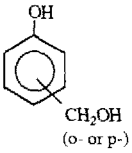
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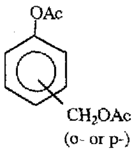
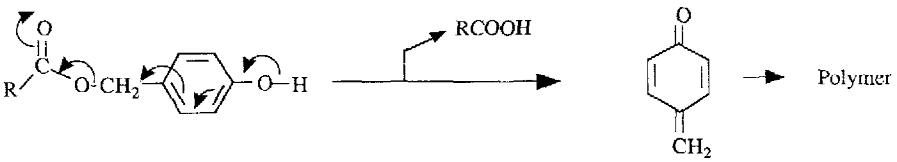

IV

The polymerisation results from the formation of a highly reactive quinone methide obtained on elimination of carboxylic acid.

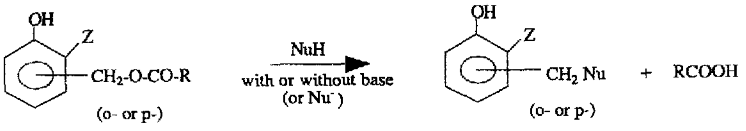


Quinone methides are intermediates frequently used in synthesis.[5] Being vinylogs of unsaturated conjugated ketones, they give rise to numerous addition reactions. Their use is regulated by their stability. Many cannot be isolated and must be prepared *in situ* ; in this case, the choice of precursor influences the course of the reaction.

We have studied the potentiality afforded by phenols I and II in synthesis and report some examples illustrating this in the present article. The phenols are obtained by reducing the corresponding azidomethylated phenols using stannous chloride.

Our results allow the reactivity of the quinone methide precursors studied to be compared with that of precursors already described in the literature, particularly like the precursors III and IV. They show that structures of the type I and II are of definite value as raw materials.

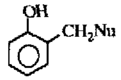
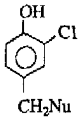
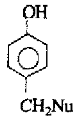
The reactions that we have carried out can be summarised by the following scheme :



Some results of condensation of alcohol, phenols and thiophenol are collected in table I. For such condensations, in particular, it appears that I and II are much more reactive than IV which requires 24 hours for the condensation of methanol under similar conditions, for example.

The condensations of azide and amines of different types can also be readily carried out, permitting the preparation of the corresponding azido and aminophenols in high yield (table 2). In the case of vinyl quinone methides, the product obtained under these conditions corresponds to the fixing of the nucleophile at the end of the pi system.[7]

Table 1. Condensation of phenols, thiophenol and alcohol

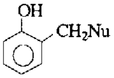
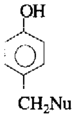
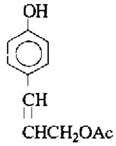
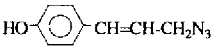
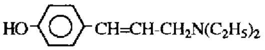
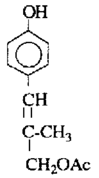
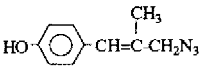
Precursor	Reagent NuH	Operating Conditions	Product[8]	Yield %	Physical properties
I (R = CH_3)	4-Ethylphenol	C_6H_6, 3 h., 25°C (a)		63 %(c)(d)	liquid
I (R = CH_3)	MeOH	0.5 h., reflux (b)		98 %(d)	liquid
II (R = CH_3, Z = Cl)	4-Ethylphenol	C_6H_6, 4 h., 25°C (a)		73 %(c)(e)	mp=124-126°C
II (R = CH_3, Z = H)	4-Ethylphenol	CH_2Cl_2, 3 h.,25°C (a)		75 %(c)(e)	mp=109°C
II (R = CH_3, Z = H)	2,4-Dichlorophenol	CH_2Cl_2, 5 h., 35°C (a)		81 %(c)(d)	liquid
II (R = CH_3, Z = H)	4-Chlorothiophenol	C_6H_6, 6 h, 50°C (a)		56 %(c)(d)	mp=66°C
II (R = CH_3, Z = H)	MeOH	0.5 h., reflux (b)		99 %(d)	liquid

(a) 1 equivalent of reagent is placed in contact with 1 equivalent of t-BuOK in 30 cc of solvent for one hour at 25°C, the precursor (5 mM) is then added and the mixture maintained at the indicated temperature for the indicated time.
(b) The precursor (5 mM) is used in an excess solution of MeOH, in the presence of 1 equivalent of sodium acetate. In the absence of sodium acetate the reaction is very slow : 80 % of the product forming after 70 hours.
(c) The nucleophile is condensed by the oxygen (or sulphur) on the CH_2 of the quinone methide.
(d) The product is purified by chromatography on silica gel.
(e) The product is purified by washing in CCl_4

Table 3 describes the condensation of some representative enolates and enols. As regards the condensations of anion malonates, the results we have obtained are better than those reported in the literature which use precursor III for example. The reactions carried out with diketones should be compared to those recently described by Poss and Belter with diketones and III in aqueous solution with no other reagent. Under the same conditions, the reaction between II and methylcyclopentanedione leads to a lower expected yield of product (compare 76 % with 97 %) but in a much shorter time (compare 1.25 h with 12 h) ; in the presence of acetylacetone and water, on the other hand, II reacts preferentially with water and is first transformed to III.

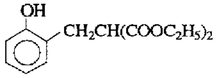
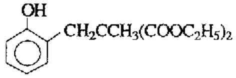
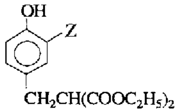
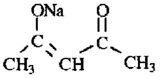
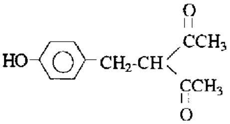
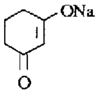
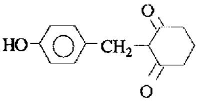
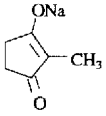
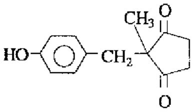
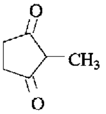
The reaction between diketone enolates and II permits the expected products to be prepared in acceptable yield under relatively mild conditions. The choice of solvent is dictated by the solubility of the diketone.

Table 2. Condensation of amines and azide

Precursor	**Reagent NuH or Nu-**	**Operating conditions**	**Product**	**: Yield %** [8]
I R = CH_3	NaN_3 (1.5 eq)	CH_3OH (30 cm^3) 2 h, reflux		65 %[a]
	$(CH_3CH_2)_2NH$ (10 cm^3)	3 h, 25°C		68 %[a]
	$C_6H_5CH_2NHCH_2CH_3$ (1 eq)	C_6H_6 (30 cm^3) 6 h, 45°C		85 %[b]
	$C_6H_5NH_2$ (1 eq)	C_6H_6 (30 cm^3) 6 h, 45°C		66 %[a] [c] (mp = 95°C)
II R = CH_3 Z = H	NaN_3 (1.5 eq)	CH_3OH (30 cm^3) 1.5 h, reflux		88 %[a]
	$CH_3CH_2NH_2$ (1 eq)	C_6H_6 (30 cm^3) 3 h, 25°C		80 %[b]
	$(CH_3CH_2)_2NH$ (10 cm^3)	3 h, 25°C		78 %[a] (mp = 95°C)
	$C_6H_5CH_2NHC_{12}H_{25}$ (1 eq)	C_6H_6 (30 cm^3) 6 h, 45°C		80 %[a] (mp = 63°C)
	$C_6H_5NH_2$ (1 eq)	C_6H_6 (30 cm^3) 6 h, 45°C		57 %[a] [c]
	NaN_3 (1.5 eq)	CH_3OH (30 cm^3) 8 h, reflux		74 %[a]
	$(CH_3CH_2)_2NH$ (2 eq)	C_6H_6 (30 cm^3) 3 h, 45°C		66 %[a]
	NaN_3 (1.5 eq)	CH_3OH (30 cm^3) 8 h, reflux		85 %[a]

(a) The product is purified by chromatography on silica gel.
(b) The product is purified by washing its solution in CH_2Cl_2 using a saturated aqueous solution of $CaCO_3$.
(c) The amine is condensed by the nitrogen on the CH_2 of the quinone methide.

Table 3. Condensation of enolates and enols

Precursor	Reagent NuH or Nu-	Operating conditions	Product : Yield % [8]	
I R = CH_3	$NaCH(COOC_2H_5)_2$ (2 eq)	THF (30 cm^3), 3 h , 25°C	40 % (a)	
		THF (30 cm^3), 3 h , 45°C	55 % (a)	
	$NaCCH_3(COOC_2H_5)_2$ (2 eq)	THF (30 cm^3), 3 h , 45°C	80 % (a)	
II R = CH_3 Z = Cl	$NaCH(COOC_2H_5)_2$ (2 eq)	THF (30 cm^3), 2 h , 25°C	72 % (a)	
II R = CH_3 Z = H		THF (30 cm^3), 3 h , 25°C	70 % (a)	
	 (2 eq)	THF (30 cm^3), 1.5 h , 45°C	64 %(a) (mp = 87°C)	
	 (2 eq)	DMF (40 cm^3), 1.5 h , 60°C	45 % (a) (mp = 172°C)	
	 (2 eq)	DMF (40 cm^3), 6 h , 70°C	76 % (b) (mp = 142°C)	
	 (1 eq)	H_2O (30 cm^3), 1.25 h , 70°C	76 % (b) (mp = 142°C)	

(a) The product is purified by chromatography on silica gel.

(b) The coarse product obtained, after hydrolysis, by extraction with CH_2Cl_2 was purified by AcOEt extraction, evaporation, then washing in Et_2O.

References and notes

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