2-CYANO-6-METHOXYTETRAHYDROPYRAN, A USEFUL PROTECTED CYANOHYDRIN FOR 2-SUBSTITUTED CYCLOHEXENONE SYNTHESIS[+]

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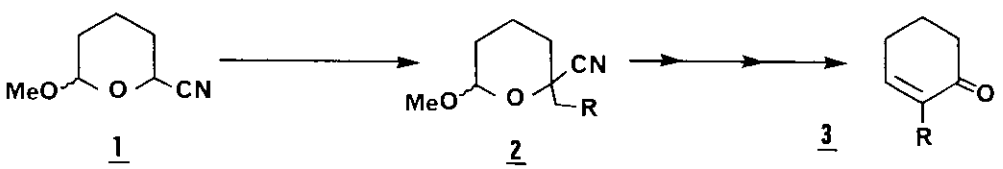
Abstract — The title compound 1, easily prepared from commercially available glutaraldehyde, is a protected cyanohydrin useful as synthon for the preparation of 2-substituted cyclohexenones.

The protected cyanohydrin reagents were introduced by Stork[1] in 1971 as useful acyl carbanion equivalents and since then a number of applications have been reported[2], including the synthesis of natural products[3].
In this paper we wish to report that the anion of 2-cyano-6-methoxytetrahydropyran 1, a kind of protected cyanohydrin, can be easily alkylated with a variety of primary alkyl halides to give compounds 2 and these can be converted to 2-substituted cyclohexenones 3 in moderate yields :



ALKYLATION OF THE ANION OF 1 (1 to 2) : A solution of 8 mmol of lithium diisopropyl amide in 40 ml of dry THF was prepared in the usual manner (n-butyllithium and diisopropylamine). To this stirred solution, cooled at -75° under nitrogen, was added dropwise a solution of 1[4] (7.1 mmol) in 1 g of dry HMPA. The pale green solution of the anion thus formed was stirred for 30 min and 1.5 equivalents of

[+]Dedicated to Professor Gilbert Stork on occasion of this 65th birthday.

the alkyl halide in THF was added dropwise. After stirring for ≃ 1 h at -75°C and additional 1-3 h at room temperature, it was quenched with H_2O. The THF was removed at reduced pressure and the product isolated in the usual manner (Et_2O or AcOEt). Purification of the crude product was conveniently done by filtration through SiO_2 gel (hexane-AcOEt mixture as eluent). Yields of purified products were usually in the 50 - 70 % range (see table I).

TABLE I

ALKYLATION OF THE ANION OF 1 WITH PRIMARY HALIDES

	ALKYL HALIDE	COMPOUND 2	YIELD
1.	n-pentyl bromide	R = $(CH_2)_3CH_3$	61 %
2.	isobutyl bromide	R = $CH(CH_3)_2$	64 %
3.	methallyl chloride	R = $C(CH_3)=CH_2$	51 %
4.	5-bromo-2-methyl-2-pentene	R = $CH_2CH=C(CH_3)_2$	44 %
5.	2-phenylethyl bromide	R = $CH_2C_6H_5$	69 %
6.	2-(m-methoxyphenyl)-ethyl bromide	R = $CH_2C_6H_4(m\text{-}OCH_3)$	62 %
7.	2-methoxyethoxymethyl chloride	R = $OCH_2CH_2OCH_3$	86 %
8.	bromoacetaldehyde diethyl acetal	R = $CH(OC_2H_5)_2$	50 %
9.	bromoacetaldehyde ethylene acetal	R = $CH(OCH_2)_2$	46 % (a,b)
10.	3-bromopropionaldehyde ethylene acetal	R = $CH_2CH(OCH_2)_2$	50 % (a)

a : Yields corrected for recovered 1; b ; Compound $BrCH=CHOCH_2CH_2OH$ was also isolated in this reaction.

As expected, the highly reactive halide MEM chloride (entry 7) gave the higher yield (86 %) while unreactive substrates such as halo ketals (entries 8, 9 and 10) gave lower yields due to side reactions with partial recovery of some starting materials. Interestingly, homoallylic and homobenzylic halides (entries 4, 5 and 6), which are easily dehydrohalogenated, gave the corresponding alkylated products in good yields. It is also worth mention that all these alkylated products 2

showed in ^{1}H-nmr spectroscopy only one OCH_3 group and a doublet of doublets (J_1 = 2 Hz, J_2 = 8-9 Hz) in δ 4.60-4.90 for the tetrahydropyran acetal proton, which strongly suggests that they were obtained as single diastereoisomers with an equatorial OCH_3 group.

2-SUBSTITUTED CYCLOHEXENONES FORMATION (2 to 3) : To 0.5-0.6 g of alkylated product 2 in 20 ml of THF, was added 5 ml of 15 % aqueous H_2SO_4 and a few drops of AcOH to render the solution homogeneous. The reaction mixture was heated under reflux for ≃ 16 h and at this point the intermediate hemiacetal 4 can be isolated if desired. Usually they were converted, without prior isolation, to the corresponding 2-substituted cyclohexenones 3 by cooling in an ice bath and addition of KOH pellets until at pH ≃ 10 was reached. It was allowed to reflux for ≃1 h, the volatiles removed under reduced pressure and the products isolated in the usual manner (Et_2O). When necessary, crude products were purified by preparative tlc (hexane-AcOEt mixtures as eluent). Cyclohexenones 3 were obtained in 40-60 % yields (see table II)

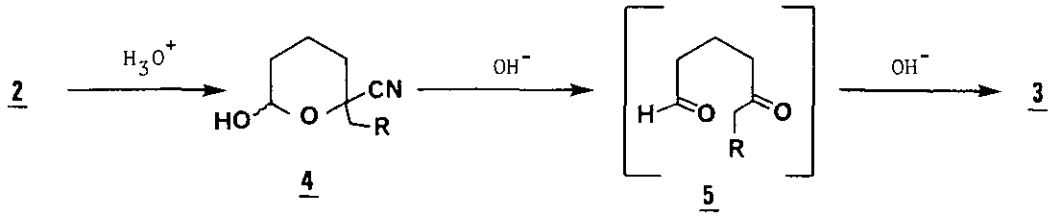
TABLE II

SYNTHESIS OF 2-SUBSTITUTED CYCLOHEXENONES

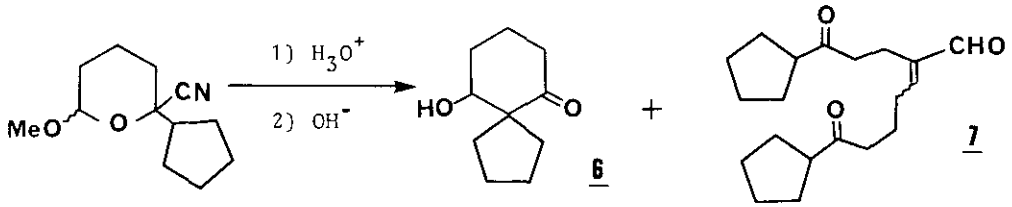
	CYCLOHEXENONES 3	YIELD
1.	R = $(CH_2)_3CH_3$	60 %
2.	R = $CH(CH_3)_2$	40 %
3.	R = $C(CH_3)=CH_2$	43 %
4.	R = $CH_2CH=C(CH_3)_2$	46 %
5.	R = $CH_2C_6H_5$	44 %
6.	R = $CH_2C_6H_4(m\text{-}OCH_3)$	52 %
7.	R = $OCH_2CH_2OCH_3$	43 %

Although the conversion of 2 to 3 should involve compounds 4 and 5 as intermediates, at present only hemiacetals 4 have been isolated. Apparently under the above described basic conditions, the 5-keto aldehydes 5 cyclize rapidly to the 2-substituted cyclohexenones 3. Milder basic conditions (e.g. rt) left unchanged hemiacetals 4. On the other hand the vigorous acid conditions required for the hydrolysis of the tetrahydropyran acetal, showed no selectivity with other acid sensitive groups present and thus the alkylated compounds 2 of entries 8, 9 and 10 of ta-

ble I gave complex mixtures under the aforementioned general conditions.



Finally, the alkylation of the anion of 1 with secondary halides was also studied. A good yield of alkylated product 2 (R = C_5H_9) was obtained with cyclopentyl bromide (62 %), but when submitted to the acid hydrolysis-KOH treatment sequence, a mixture was obtained from which compounds 6 and 7 were isolated in low yields :



We hope this method will be a complementary valuable addition to other recent methods for the synthesis of 2-substituted cyclohexenones[5].

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REFERENCES AND NOTES

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2. For a review see : J.D. Albright, Tetrahedron, 1983, 39, 3207.
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4. Compound 1 was obtained in 50-60 % yield from aqueous glutaraldehyde by monocyanohydrin formation (NaCN, AcOH), followed by acetalization of the intermediate hemiacetal with TosOH and MeOH (rt, overnight).
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