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CONDENSATION OF 1,4-DIOLS TO TETRAHYDROFURANS INDUCED BY N,N-DIETHYLPHOSPHORAMIDIC DICHLORIDE[1]

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A simple and efficient procedure has been developed for the condensation of 1,4-diols to tetrahydrofurans using N,N-diethylphosphoramidic dichloride as a reagent.

We have recently reported (1) that alcohols react with N,N-dimethylphosphoramidic dichloride (2) in refluxing 1,2-dimethoxyethane to give amidate derivatives of general formula ROPO(Cl)-$N(CH_3)_2$ which subsequently undergo elimination or displacement reaction by chloride ion yielding olefins or alkyl chlorides respectively. In the presence of a suitable nucleophilic center, it is conceivable that an intramolecular replacement could proceed preferentially leading to cyclic products according to the following scheme:

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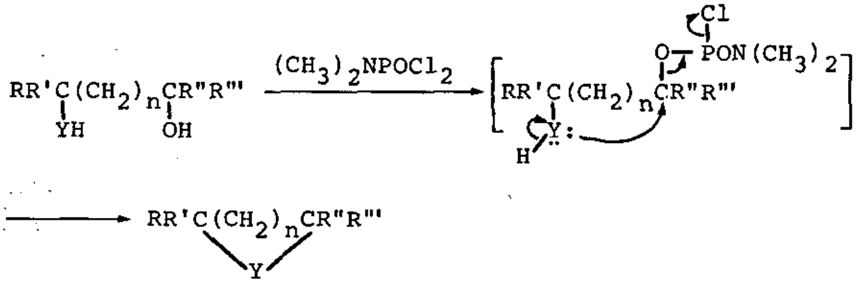
[1] Dedicated to Professor T. Nozoe on the occasion of his 77th birthday.



Of particular interest is the introduction of a cyclic ether linkage from 1,4-diols (Y=O; n=2), a process of considerable synthetic utility.

Toward this end, a number of diols were subjected to treatment with *N*,*N*-dimethylphosphoramidic dichloride under various conditions. The anticipated condensation did indeed occur but the best yields obtained for the corresponding tetrahydrofuran derivatives were only in the range of 50-60%. Further investigation toward improvement of the efficiency of the transformation led to the recognition of the *N*,*N*-diethyl analogue[2] as a superior reagent and the development of a simple procedure for the condensation of 1,4-diols. In a typical experiment, a solution of 4-(1-hexyl)-1,4-decanediol (220 mg, 0.85 mmol) and *N*,*N*-diethylphosphoramidic dichloride (800 mg, 4.25 mmol) in 1,2-dimethoxyethane (10 ml) was refluxed under a nitrogen atmosphere

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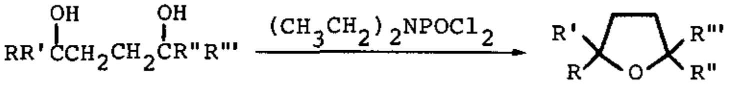
[2] *N*,*N*-Diethylphosphoramidic dichloride, bp 101°C/12 torr, was prepared from diethylamine and phosphorus oxychloride in a manner analogous to the preparation of *N*,*N*-dimethylphosphoramidic dichloride (3).

for 10 hr. After cooling to room temperature, the reaction mixture was poured into water (40 ml) and extracted with ether (3 x 40 ml). The combined extracts were dried over magnesium sulfate, filtered, and concentrated. Silica gel column chromatography of the residue eluting with a solution of 10% ether in pentane afforded 148 mg (72% yield) of 2,2-di-(1-hexyl)tetrahydrofuran: ir (film) 1065 cm^{-1} (ether); nmr (CCl_4) δ 0.90 (br.t, 6H, J = 4 Hz, $-CH_3$) and 3.68 (br.t, 2H, J = 6 Hz, $-CH_2O-$). Anal. calcd. for $C_{16}H_{32}O$: C 79.93, H 13.42; found: C 80.19, H 13.48.

Eleven diols were studied and the generality of the procedure is apparent from the results summarized in the Table. In addition to operational simplicity, an especially promising feature is that the reaction is independent of the substitution pattern. Under mild conditions, the procedure was found to be effective for a wide variety of 1,4-diols ranging from simple ones in which both carbinol moieties are primary (Entries 1-3) to the heavily substituted tertiary-tertiary type (Entry 11).

The condensation of 1,4-diols represents an important process for the preparation of tetrahydrofuran derivatives. The available general methods (4) for such condensations are however limited in number and often require crucial reaction conditions and/or multi-step operation. The forgoing report describes a convenient direct procedure which should prove to be synthetically useful.

Table. Condensation of 1,4-Diols



$$RR'\overset{OH}{C}CH_2CH_2\overset{OH}{C}R''R''' \xrightarrow{(CH_3CH_2)_2NPOCl_2} $$

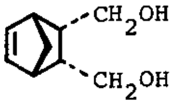
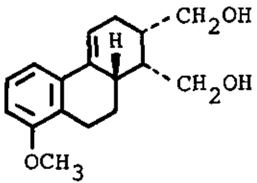
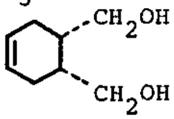
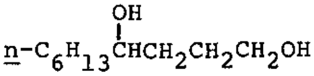
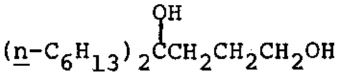
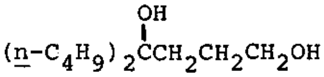
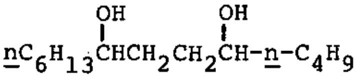
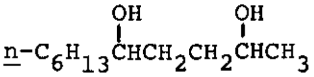
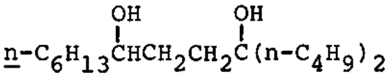
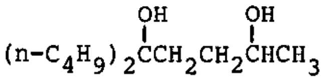
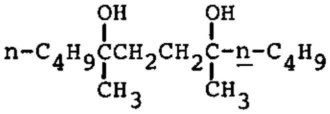
Entry	Type	Diol	Time (hr)	Yield (%)[a]
1	1°-1°		7	70
2			4.5	90
3			3	40(>86[b])
4	1°-2°	 $n\text{-}C_6H_{13}\overset{OH}{C}HCH_2CH_2CH_2OH$	22	66
5	1°-3°	 $(n\text{-}C_6H_{13})_2\overset{OH}{C}CH_2CH_2CH_2OH$	10	72
6		 $(n\text{-}C_4H_9)_2\overset{OH}{C}CH_2CH_2CH_2OH$	10	73
7	2°-2°	 $nC_6H_{13}\overset{OH}{C}HCH_2CH_2\overset{OH}{C}H\text{-}n\text{-}C_4H_9$	8	86[c]
8		 $n\text{-}C_6H_{13}\overset{OH}{C}HCH_2CH_2\overset{OH}{C}HCH_3$	9	83[c]
9	2°-3°	 $n\text{-}C_6H_{13}\overset{OH}{C}HCH_2CH_2\overset{OH}{C}(n\text{-}C_4H_9)_2$	24	68
10		 $(n\text{-}C_4H_9)_2\overset{OH}{C}CH_2CH_2\overset{OH}{C}HCH_3$	12	77

Table (continued)

Entry	Type	Diol	Time (hr)	Yield (%)[a]
11	3°-3°	 $n\text{-}C_4H_9\underset{CH_3}{\overset{OH}{C}}CH_2CH_2\underset{CH_3}{\overset{OH}{C}}\text{-}n\text{-}C_4H_9$	36	65[c]

[a] Yields are for isolated products of analytical purity and are not optimized. [b] Determined by GLC. [c] Products were obtained as a mixture of two stereoisomers.

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