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Studies on the Reactions of HOBt, HOOBt, HOSu with Dichloroalkane Solvents

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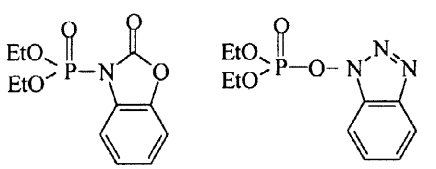
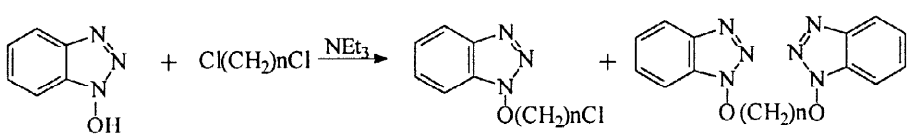
Abstract: The well known peptide synthesis reagents HOBt, HOOBt and HOSu were found to react with chloroalkane solvents in the presence of triethylamine. Six new compounds were obtained and characterized.

1-Hydroxybenzotriazole (**HOBt**), 3-hydroxy-4-oxo-3,4-dihydro-1,2,3-benzotriazole (**HOOBt**) and N-hydroxy succinimide (**HOSu**) are among the most widely used **reagents** in peptide synthesis. They are often used to activate the carboxyl group and inhibit racemization in the peptide coupling process[1]. Previously, we successfully prepared a coupling reagent diethylphosphoryl benzoxazolone[2] (**DEPBO, 1**) using CH_2Cl_2 as a solvent and Et_3N as a base. However, when **HOBt** was subjected to similar reaction conditions, the reaction did not give the desired product **DEOBt (2)**, but two new compounds **4a** and **4b** were obtained.



DEPBO(1) **DEOBt(2)**



3 **4a, n=1** **5a, n=2** **4b, n=1** **5b, n=2**

Though the reactions of **HOBt** with dihaloalkanes under strongly basic conditions have been reported[3], there is no report of such reactions occurring under normal peptide coupling conditions. Since CH_2Cl_2 and Et_3N are commonly used in peptide synthesis, we studied and report here the reaction of **HOBt**, **HOOBt** and **HOSu** with CH_2Cl_2 and 1,2-dichloroethane using Et_3N as a base (Table 1). The reaction between **HOBt** and CH_2Cl_2 in the presence of Et_3N was a slow process at room temperature (entry 1). A higher product yield was obtained when the reactions were performed at elevated temperature (entry 2) and for extended reaction time (entry 3). While the reaction between **HOBt** and $ClCH_2CH_2Cl$ afforded a low yield of **5a** at room temperature,

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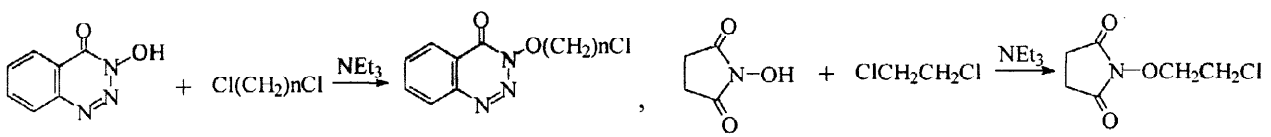
moderate yield of **5a** can be obtained at an elevated temperature (entry 6, 7). **HOOBt** was also found to react with CH_2Cl_2 and $ClCH_2CH_2Cl$ to a certain extent (Scheme 1). **HOSu** did not react with CH_2Cl_2 in the presence of NEt_3 at room temperature, but **HOSu** can react with $ClCH_2CH_2Cl$ to provide the monosubstituted product **10** in good yield (entry 10). Interestingly, though **HOBt** tends to form disubstituted product **4b** with CH_2Cl_2, monosubstituted products were obtained when 1,2-dichloroethane was used as a solvent.

Table 1. Reactions of HOBt, HOOBt, HOSu with Dichloroalkane Solvents

Entry	Reactants (10 mmol)	Solvent (20 ml)	Et_3N (ml)	Tempera -ture(℃)	Time (hr)	Products (yield %)	m.p. (℃)
1	HOBt	CH_2Cl_2	2	20	48	**4b** (0.9)	**4b**,186-187
2	HOBt	CH_2Cl_2	2	40	48	**4a** (20), **4b** (37)	**4a**,42-44, **4b**,186-187
3	HOBt	CH_2Cl_2	2	20	168	**4b** (9.9)	**4b**, 186-187
4	HOBt	CH_2Cl_2	4	20	48	**4a** (16.7), **4b** (28.4)	**4a**,42-44, **4b**,186-187
5	HOBt	$ClCH_2CH_2Cl$	2	20	48	**5a** (9.9), **5b** (trace)	**5a**, 49-50, **5b**, 94-95
6	HOBt	$ClCH_2CH_2Cl$	2	40	48	**5a** (55.2)	**5a**, 49-50
7	HOBt	$ClCH_2CH_2Cl$	4	40	48	**5a** (55.3)	**5a**, 49-50
8	HOOBt	CH_2Cl_2	2	20	48	**7** (18.7)	**7**, 132-134
9	HOOBt	$ClCH_2CH_2Cl$	2	20	48	**8** (19.4)	**8**, 113-114
10	HOSu	$ClCH_2CH_2Cl$	4	35	48	**10** (71.5)	**10**, 108-110



6 **7, n=1** **8, n=2** **9** **10**

Scheme 1

In summary, we found that the peptide coupling additives **HOBt, HOOBt** and **HOSu** react with dichloroalkanes in the presence of Et_3N. All of the products were purified by silica gel chromatography and all new compounds were fully characterized. These reactions may form by-products if these dichloroalkanes were used as solvents in peptide coupling.

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REFERENCES:

1. Anderson, G. W.; Zimmerman, J. E.; Calahan, F. M. *J. Am. Chem. Soc.* **1963**, 85, 3039.
2. Zhang, Deyi; Ye, Yunhua in *Peptide: Biology and Chemistry,* Du, Y.-C., Ed, Science Press, Beijing, **1991**; pp235-236.
3. Feld, W. A.; Evans. D. G. *J. Chem. Eng. Data,* **1983**, 28, 138-139.