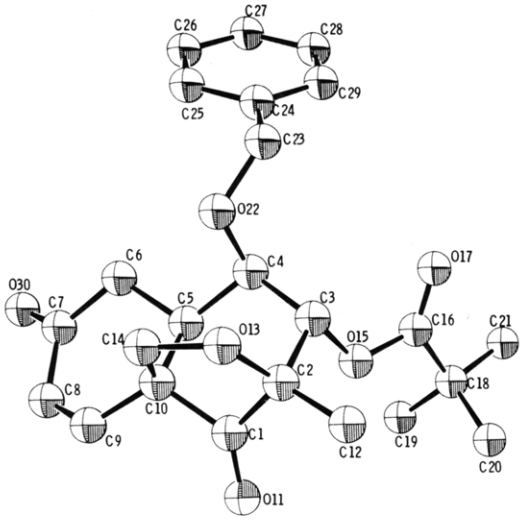


**Figure 1.**

yield.[8] Admixture of **6** (1 equiv) with 6 N $H_2SO_4$ (0.1 M in THF at 40 °C for 12 h) both established the furanone ring[9] and removed the acetonide residue to afford **7** in 81% yield (mixture of anomers).

Without purification of intermediates, **7** was converted into the unsaturated ketone **8**. Degradation of the lactol moiety of **7** (1 equiv/0.5 M in THF) into its corresponding $\beta$-hydroxy aldehyde was accomplished through the agency of $NaIO_4$ (0.2 M, buffered with $NaHCO_3$, 0.2 M at 0 °C). The latter material (1 equiv, 0.2 M in toluene) was immediately reacted with 1-(triphenylphosphoranylidine)-2-propanone (1.4 equiv at 40 °C for 12 h). Finally, the crude $\delta$-hydroxy-$_{\alpha,\beta}$-unsaturated methyl ketone (1 equiv, 0.2 M in pyridine) was reacted with trimethylacetyl chloride (15 equiv) and 4-DMAP (0.2 equiv) to give **8** $[\alpha]_D$ + 147.15° (*c* 2.00, $CH_2Cl_2$) in 68% overall yield from **7**.

We now faced the problem of chemically redefining **8** into a species containing diene and dienophilic residues suitable for intramolecular cycloaddition. To this end, we converted the side chain of **8** (1 equiv, 0.2 M in $Et_2O$) using $Et_3N$ (3.5 equiv) and TBSOTf (1.75 equiv) into its corresponding silyl enol ether diene analogue.[10] This substance (1 equiv, 0.2 M in $Et_2O$ at −78 °C) was then treated with L-Selectride (Aldrich) (1.05 equiv) followed by workup with unsaturated $NH_4Cl$ to afford **9**, $[\alpha]_D$ +29.85° (*c* 1.34, $CH_2Cl_2$), in 80% overall yield from **8**.[11] Emboldened by the survival of the silyl enol ether residue, we decided to submit it to the reaction guantlet necessary to realize $_{\alpha}$-methylenation of the furanone residue. **9** (1 equiv) dissoleved in $HCO_2Et$ (0.2 M) was treated with NaH (2.5 equiv) and EtOH (0.1 equiv).[12] After workup, the crude reaction product (1.0 equiv in acetone, 0.2 M) was treated with $K_2CO_3$ (1.3 equiv) and dimethyl sulfate (2.0 equiv) to give **3** as an oil.[13]

The moment of truth in this synthetic scheme was upon us, but out first efforts to achieve intramolecular closure of **3** in an exo-cyclic mode were less than memorable. For example, at 95 °C in toluene, **3** gave a 4:1 mixture of Diels-Alder adducts in low yield. Detailed examination of the $^1H$ spectrum of these substances did hold some promise in that the spectrum of the major isomer exhibited coupling patterns indicative of the desired exo-cycloaddition adduct **2**.[14] In an effort to enhance both the yield and the selectivity of cycloaddition, we undertook an examination of the influence of Lewis acids on the reaction. Eventually, it was found that treatment of crude **3** (1.0 equiv) in $CH_2Cl_2$ (0.2 M at −20 °C) with $Al(CH_3)_3$ (1.1 equiv) gave, after standard workup and chromatography, only the exo-adduct **2** as a low-melting solid, $[\alpha]_D$ +80.00° (*c* 2.16, $CH_2Cl_2$), in 62% overall yield from **9**; 24% overall yield from the methyl ketone **5** (10 steps).

In addition to a detailed spectrscopic analysis of **2**, we further satisfied ourselves of its structure by hydrolysis of the molecule in dioxane containing aqueous $H_2SO_4$ to obtain the diketone **10** in 70% yield, $[\alpha]_D$ +75.00° (*c* 1.14, $CH_2Cl_2$). This crystalline substance (mp 127.5–129 °C) was submitted to X-ray analysis which conclusively demonstrated its stereochemistry (Figure 1).[15]

**Acknowledgment.** We thank L. Symon and C. Poss for help in large-scale preparations of early synthetic intermediates. Financial support from the NIH and the Merck Corp. are gratefully acknowledged.

**Supplementary Material Available:** X-ray crystal structure data and tables of fractional coordinates and temperature factors, bond lengths, and bond angles (6 pages). Ordering information is given on any current masthead page.

(7) For an excellent discussion of this and related phenomenon, see: Ahn, N.-T. *Top. Curr. Chem.* **1980**, *88*, 145.

(8) The new componds cited in this manuscript gave satisfactory $^1H$ (300 and 400 MHz) and $^{13}C$ NMR IR, and mass spectra. Those intermediates that were stable gave correct elemental analyses.

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(11) Ganem, B.; Fortunato, J. M. *J. Org. Chem.* **1975**, *40*, 2846. Ganem, B.; Fortunato, J. M. *Ibid.* **1976**, *41*, 2194.

(12) Trace quantities of ethanol seem to be essential to this reaction.

(13) The geometry of the vinylogous ester **3** is assigned on the basis of work described by: Lubineau, A.; Malleron, A. *Tetrahedron Lett.* **1984**, *25*, 1053.

(14) These coupling patterns were calculated both from molecular models and from MM2 calculations using a program kindly provided us by Professor W. C. Still (Columbia University).

(15) Details available in the form of supplementary material.

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## 1,2,2,2-Tetrachloroethyl *tert*-Butyl Carbonate: A Simple and Efficient Reagent for the *tert*-Butoxycarbonylation of Amines and Amino Acids

*Summary:* The reaction of 1-chloroalkyl carbonates with amines affords good yields of the corresponding carbamates. Application to the BOC protection of amino acids is described.

*Sir:* Since its discovery in 1957,[1] the *tert*-butoxycarbonyl (BOC) group has become the most important amino protecting group in peptide synthesis. Unfortunately, the

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0022-3263/85/1950-3951$01.50/0 

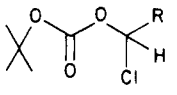
Table I. Preparation of *N*-BOC Amines and Amino Acids

| amine | reagent | reaction condition[a] | yield,[b] % | bp °C/torr mp, °C | $[\alpha]^{20}_D$ | lit. data[2,9,10] (mp, °C; $[\alpha]^{20}_D$) |
|---|---|---|---|---|---|---|
| $PhCH_2NH_2$ | 1 | A 1 h | 58 | 103/0.5 53 | | 53–54 |
| | 2 | A 1 h | 91 | | | |
| imidazole | 1 | A 1 h | 50 | 64/1 | | 44.5–47 |
| | 2 | A 1 h | 86 | | | |
| Gly | 1 | B 24 h | <7 | | | |
| | 2 | B 6 h | 86 | 85–88 | | 88–89 |
| L-Ala | 2 | B 5 h | 90 | 80–81 | −24, *c* 2.1 AcOH | 83–84, −22.4; *c* 2.1AcOH |
| L-Phe | 2 | B 5 h | 79 | 85–87 | +28, *c* 1.5 EtOH | 85–87; +24.7; *c* 1.5 EtOH |
| L-Pro | 2 | B 5 h | 91 | 132–133 | −60, *c* 2.0 AcOH | 136–137; −60.2; *c* 2.0 AcOH |
| L-Tyr | 2 | B 6 h[c] | 82 | 206[d] | +32, *c* 1.8 MeOH | 215–217; |
| L-Asp | 2 | B 24 h | 60 | 117–119 | −5, *c* 1.0 MeOH | 118–119; −6.2; *c* 1.0 MeOH |
| L-Ser | 2 | B 24 h | 78 | 139–140[d] | +8, *c* 2.8 MeOH | 142–144; +13; *c* 3.0 MeOH |

[a] 1 to 1.1 equiv of 1 or 2 was used in A, 1 M concentration in THF/saturated $K_2CO_3$ (3/1) at 20 °C; B, 1 M concentration in dioxane/$H_2O$ (1/1), $Et_3N$ (3 equiv) at 20 °C. [b] Yields are given for isolated materials with the physical data reported. [c] Method B with 1 equiv of $Et_3N$ and 1.5 equiv of NaOH. [d] Isolated as the DCHA salts.

synthesis of BOC amino acids using *tert*-butyl chloroformate is impractical because of the instability of that reagent. Many other reagents have been proposed to effect BOC protection,[2] the search for simple, stable, harmless, and cheap reagents being a constant preoccupation of investigators.

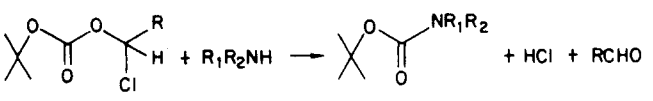
While studying the synthetic potential of 1-chloroethyl ethyl carbonate, we found that it readily reacts with amines at the carbonyl function to give the corresponding ethyl carbamates in good to excellent yield. With this result we thought that 1-chloroalkyl *tert*-butyl carbonates **1** and **2** should be valuable reagents for the BOC protection of amines.



**1**, R = $CH_3$
**2**, R = $CCl_3$

The carbonates are easily prepared in quantitative yields from 1-chloroalkyl chloroformates and *tert*-butyl alcohol by simple procedures.[3] The recent availability[4] of these two long known chloroformates provides an easy access to this type of reagent.

Reagent **1** is a medium boiling liquid (bp 88 °C/(20 torr)) stable for years at room temperature, while **2** is a distillable crystalline solid (mp 70 °C) which is stable for weeks at room temperature and for months in the refrigerator. Both react with amines under mild conditions to give the carbamate, HCl, and the corresponding aldehyde.



When **1** is reacted with primary amines, the formation of acetaldehyde and its consequent reaction with the starting amine considerably lowers the yield. Moreover, **1** is not reactive enough to easily effect the BOC protection of amino acids.[6] However, we found that substitution of the methyl by a trichloromethyl group sufficiently increases the electrophilicity of the carbonyl to lead to almost quantitative yields of carbamates starting from model amines (see Table I). Furthermore, **2** satisfactorily reacts with various amino acids in standard conditions. The reaction medium then is freed from excess reagent and byproducts by extraction with ether, and the BOC amino acids are easily obtained by conventional extraction and crystallization procedures. Reagent **2** is especially useful in the case of unprotected hydroxy amino acids as exemplified by the synthesis of BOC-L-serine and BOC-L-tyrosine. Furthermore, it reacts satisfactorily with L-aspartic acid and L-serine, two amino acids known to be inert to the action of *tert*-butyl *p*-nitrophenyl carbonate.[7] Although the reaction time is longer, the yields are comparable to those obtained with popular di-*tert*-butyl dicarbonate or *tert*-butyl fluoroformate.[8] Also, no higher peptide byproducts were detected in any of the reactions.

This should make 1,2,2,2-tetrachloroethyl *tert*-butyl carbonate (BOC-OTCE) a promising reagent for the protection of amines and amino acids. It is crystalline, stable, nontoxic, and last but not least, it considerably reduces the cost of a BOC equivalent.

**Registry No.** **1**, 98015-51-1; **2**, 98015-52-2; $PhCH_2NH_2$, 100-46-9; $PhCH_2NHBoc$, 42116-44-9; Gly, 56-40-6; L-Ala, 56-41-7; L-Phe, 63-91-2; L-Pro, 147-85-3; L-Tyr, 60-18-4; L-Asp, 56-84-8; L-Ser, 56-45-1; Boc-Gly, 4530-20-5; Boc-L-Ala, 15761-38-3; Boc-L-Phe, 13734-34-4; Boc-L-Pro, 15761-39-4; Boc-L-Tyr·DCHA, 16944-14-2; Boc-Yl-Asp, 13726-67-5; Boc-Yl-Ser, 3262-72-4; imidazole, 288-32-4; *N*-Boc-imidazole, 49761-82-2; chloral, 75-87-6; phosgene, 75-44-5; 1,2,2,2-tetrachloroethyl chloroformate, 98015-53-3; 1-chloroethyl chloroformate, 50893-53-3.

**Supplementary Material Available:** Full experimental details describing the synthesis of reagents **1** and **2** and a typical

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(3) Pyridine (1 equiv) is slowly added to a cooled (0 °C) solution of *tert*-butyl alcohol and 1,2,2,2-tetrachloroethyl chloroformate (1 equiv each) in dichloromethane. The reaction medium is stirred at room temperature for 4 h. Washing with water and evaporation of the solvent gives crystalline **2** in nearly quantitative yield. Recrystallization is effected from hexane (mp 68–70 °C, 87% yield).

(4) Chloral (1.0 equiv) is added to a stirred mixture of liquid phosgene (~1.1 equiv) and $PhCH_2N^+(Bu)_3Cl^-$ (0.05 equiv, reusable) (dry ice condenser to trap refluxing phosgene). After 1 h, excess phosgene is removed by aspiration. The crude material (quantitative yield by NMR) can be used as is. Distillation at low temperature (40–47 °C, 4 mm) gives 70% yield of pure product. Note: Review phosgene safety precautions before repeating! Cagnon, G.; Piteau, M.; Senet, J. P.; Olofson, R. A.; Martz, J. T. Eur. Pat. Appl. E.P. 40,153 (issued 18-11-81); *Chem. Abstr.* **1982**, *96*, 142281y.

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procedure for the synthesis of BOC amino acids (3 pages). Ordering information is given on any current masthead page.

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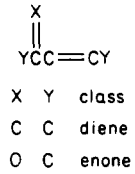
## Irradiation of 1,3-Dienes in the Presence of Anilines

*Summary:* Acetonitrile solutions of 1,3-cyclohexadiene or 2,5-dimethyl-2,4-hexadiene and aniline, its N-methylated derivatives, $Et_2NH$, or $Et_3N$ were irradiated at 350 nm. Adducts (3-anilinoalkenes) were observed in the presence of the primary or secondary anilines but not with the tertiary aniline or the alkylamines. These products are interpreted as arising via an electron-transfer intermediate within the singlet manifold. The cyclic diene gives competitive [2 + 2] and [4 + 2] dimerization apparently via the triplet. A third diene cyclooctadiene gave no observable chemistry in appreciable amounts.

*Sir:* Molecules undergo an interesting and useful change in redox properties upon electronic excitation that allows them to undergo electron-transfer reactions in the presence of suitable donors or acceptors.[1] We have explored the use of amines as donors in conjunction with enones as the combination chromophore/acceptor.[2-6] Cyclic enones react very readily in this sense to give 1:1 adducts albeit via a mechanism replete with numerous excited states and transient intermediates.[6] We were intrigued by the idea that various analogous four-$\pi$-electron systems should give similar behavior and have examined a number of them.

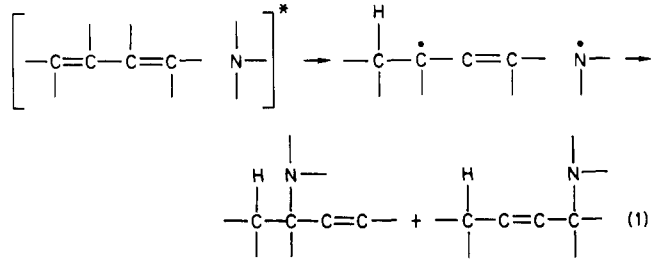


| X | Y | class |
|---|---|---|
| C | C | diene |
| O | C | enone |

The Weller equation predicts that the ability to undergo electron transfer simply requires an exothermic balance to the sum of the following terms: excited-state energy level; ionization potential; electron affinity; coulombic work term.[1] Thus, one predicts such a reaction for amines with dienes and enones in spite of the fact that they react via different lowest excited states and preferred multiplicities. We herein report on the results from irradiation of a number of 1,3-dienes with amines.

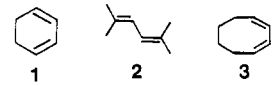
It is instructive to begin with a consideration of the energetics. The diene singlet and triplet are approximately 97 and 55 kcal/mol above the ground state, respectively.[8] The reduction potentials for dienes are −2.6 V (62 kcal/mol) vs. SCE, while the anodic potentials for DABCO, $PhNMe_2$, and $Et_3N$ are +0.45, 0.68, and 1.15 V (10, 16, and 27 kcal/mol), respectively.[9] The coulombic term is 2.5 kcal/mol in $CH_3CN$, assuming an interionic distance of 3.5 Å. These simple and approximate calculations predict that electron transfer between the diene triplet and any of the three amines is endergonic by at least 12 kcal/mol. The reaction is favored with the diene singlet in the range −8 to −26 kcal/mol for the same three. Aniline has $E_s$ = 97 kcal/mol and $E_T$ = 77 kcal/mol,[8] and the reaction is predicted to be energetically allowed by the same amount as the diene singlet from its singlet (−20 kcal/mol) and approximately isoenergetic when considering the amine triplet (−1 kcal/mol). On the basis of the uncertainty of the electrochemical data and these calculations, one can probably assume that the diene triplet is unreactive under all circumstances toward this kind of behavior while the diene singlet will react with arylamines (or DABCO) and may be borderline with aliphatic ones. Likewise, aniline singlets are reactive toward all dienes, while the aniline triplet is borderline toward cyclohexadiene **1** and more unreactive toward the acyclic ones or any others with a higher triplet energy than 1.

We were encouraged by the synthetic results of Jolidon and Hansen,[10] who reported high-yield photochemical reactions between dienes and anilines. They examined the behavior of about a dozen dienes of various structures in the presence of aniline, *N*-methylaniline, and some substituted analogues using the output of a 125-W Hg arc. A charge-transfer intermediate or state was invoked, but no mechanistic studies were reported. Unsymmetrical dienes give at least two isomeric diene–aniline adducts which are consistent with the protonation of the diene terminal carbon that represents the most stable anion followed by coupling of the resultant radicals at the two unequivalent allylic positions. This is shown in eq 1, where the first species is an electron- or charge-transfer intermediate.



(1)

We chose to irradiate cyclohexadiene (**1**), 2,5-dimethyl-2,4-hexadiene (**2**), and 1,3-cyclooctadiene (**3**) as examples of a constrained cyclic, an acyclic, and a cyclic capable of cis–trans isomerization. Amines include aniline



1 2 3

(**4**), *N*-methylaniline (**5**), *N*,*N*-dimethylaniline (**6**), triethylamine (**7**), and diethylamine (**8**). The similar absorption vs. wavelength profiles for the dienes and amines made preparation of samples where one or the other exclusively absorbs light virtually impossible, but we were generally able to make one dominant by judicious choice

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(6) For a complete discussion of the photoreactions of cyclic enones with amines including laser transients, quantum yields, and concentration dependence, see: Pienta, N. J.; Culp, S. J.; McKimmey, J. E.; Smith, D. W. *J. Am. Chem. Soc.* submitted for publication.
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