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NEW REAGENTS FOR EXHAUSTIVE ALKOXYCARBONYLATION OF AMIDES AND URETHANS. DI-1-ADAMANTYL DI- AND TRICARBONATE

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Summary: Di-1-adamantyl dicarbonate, di- and tricarbonate, and di-t-butyl tricarbonate were found to be useful reagents for the DMAP-catalyzed alkoxycarbonylation of amides and urethans.

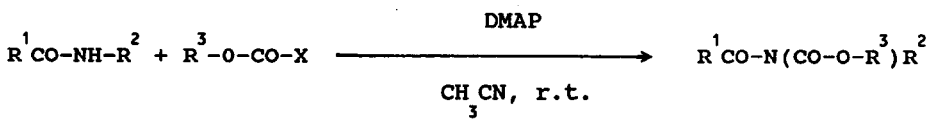
Previously it was demonstrated that a wide range of amides, urethans and similar compounds[2] can be converted to the corresponding t-butoxycarbonyl (Boc) derivatives under rather mild conditions using Boc_2O[3] as reagent and 4-dimethylaminopyridine[4] (DMAP) as catalyst. Many of the new derivatives readily undergo selective cleavage with nucleophiles.[2a,5] As furthermore recently exhaustive t-butoxycarbonylation has turned out to be preparatively useful,[6] we have now investigated some alternatives to Boc_2O as reagent and, particularly, attempted to extend the scope of this reaction to other protecting groups.

Our earlier attempts to extend this methodology to other dicarbonates have been unsuccessful. Dimethyl, dibenzyl and diallyl dicarbonate all rapidly decompose in the presence of DMAP in acetonitrile at room temperature.[2c,7] In di-1-adamantyl dicarbonate[8] ($Adoc_2O$), however, we have now found an additional species that forms a quite stable intermediate with DMAP in acetonitrile and studied this by ^1H NMR.[9] The Adoc-DMAP adduct is at least as stable as Boc-DMAP, but unexpectedly somewhat more reactive. For example, using Boc-Gly-OBzl as substrate, it reacts about twice as fast. A few amides, anilides and amino acid derivatives were reacted on a preparative scale with $Adoc_2O$ and DMAP in acetonitrile to give the corresponding Adoc-substituted compounds in yields over 90% (see Scheme).

Using di-1-adamantyl tricarbonate[8] ($Adoc_2CO_3$), the immediate precursor of $Adoc_2O$, the same Adoc-derivatives have been obtained in similar yields. ^1H NMR experiments indicated that $Adoc_2CO_3$ and $Adoc_2O$ evidently gave the same Adoc-DMAP adduct [δ_{CD3CN} 8.49 and 6.90 (2d, 4H, arom.H), 3.30 (s, 6H, Me_2N)]. 1-Adoc-pyrrole was obtained similarly from $Adoc_2CO_3$.[10]

The same was found to hold for Boc_2CO_3. In this case, in the presence of DMAP a fast conversion into Boc_2O was confirmed by ^1H NMR experiments.[11] A preparative experiment also demonstrated that Boc_2CO_3 could replace Boc_2O in the established t-butoxycarbonylation of pyrrole, thus affording the corresponding 1-Boc-derivative in a similar yield (79%).[12]

S C H E M E[13]



$R^1CO\text{-}NH\text{-}R^2 + R^3\text{-}O\text{-}CO\text{-}X \longrightarrow R^1CO\text{-}N(CO\text{-}O\text{-}R^3)R^2$

(1) (2) (3)

	R^1	R^2	R^3	X
a;	Me	Ph	1-adamantyl	$O\text{-}CO\text{-}O\text{-}R^3$
b;	1-adamantyloxy	Ph	1-adamantyl	$O\text{-}CO\text{-}O\text{-}R^3$
c;	Bzl-O	Me	1-adamantyl	$O\text{-}CO\text{-}O\text{-}R^3$
d;	Bzl-O	CH(Me)COOEt	1-adamantyl	$O\text{-}CO\text{-}O\text{-}R^3$
e;	Bzl-O	$CH(CHMe_2)COOEt$	1-adamantyl	$O\text{-}CO\text{-}O\text{-}R^3$
f;	t-butoxy	$CH_2COOBzl$	1-adamantyl	$O\text{-}CO\text{-}O\text{-}R^3$
g;	Me	$CH_2COOBzl$	1-adamantyl	$O\text{-}CO\text{-}O\text{-}R^3$
h;	Me	$CH_2COOBzl$	1-adamantyl	$O\text{-}(CO\text{-}O)_2\text{-}R^3$
i;	Me	Ph_2	t-butyl	F
j;	Me	Ph	1-adamantyl	F

Kemp and Curran[14] in a recent paper rationalized the appearance of an unexpected product in terms of a Boc-OCO-DMAP adduct. In our experiments, however, we could not detect any evidence for this species.

Furthermore, the utility of alkoxycarbonylfluorides, represented by BocF[15] and AdocF[16] (which is commercially available), was examined. In

both cases the DMAP-mediated reaction with acetanilide in acetonitrile gave only 30% yields of the desired products (**3a**, **3i**). In the case of AdocF, considerable amounts of the carbonate[17] was also isolated along with the product. ^{1}H NMR studies revealed a very slow formation of the DMAP adducts from the fluorides.

Further completing experiments along these lines with particular attention to new amino acid derivatives are in progress.

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9 ^{1}H NMR in CD_3CN: DMAP δ 8.12 and 6.54 (2d,4H,pyridine), 2.95 (s,6H, Me_2N); Adoc-DMAP δ 8.49 and 6.90 (2d,4H,pyridine), 3.30 (s,6H,Me_2N).
10 1-(1-Adamantyloxycarbonyl)-pyrrole: M.p. 66 °C; ^{1}H NMR δ 7.23 (t,J=2.4, 2H), 6.20 (t,J=2.4,2H), 2.23, 1.70 (m,15H,adamantyl); ^{13}C NMR δ 148.8 (CO), 119.9 (pyrrole C2), 111.7 (pyrrole C3), 83.4, 41.3, 36.0, 30.9 (adamantyl), IR (KBr) 1741 cm^{-1} (CO).
11 When a 0.1 M solution of Boc_2CO_3 in CD_3CN [$\delta(Bu^t)$=1.53] was treated with 0.1 equiv. of DMAP at room temperature, no trace remained after 10 min. Instead Boc_2O [$\delta(Bu^t)$=1.49] appeared as the main product.
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13 Representative analytical data on new products (NMR spectra in $CDCl_3$/TMS):
Compound (**3a**)=(**3j**), Ac(Adoc)NPh: M.p. 92-92.5 °C; ^{1}H NMR δ 7.33 (s,

5H,Ph), 2.58 (s,3H,Me), 2.17, 2.00, 1.61 (m,15H,adamantyl); ^{13}C NMR δ 172.9 (COMe), 152.2 (CO), 138.8, 128.8, 128.1, 127.6 (Ph), 83.0, 41.0, 35.9, 30.7 (adamantyl), 26.5(Me); IR (KBr) 1740, 1702 cm^{-1} (CO).

Compound (**3b**), Adoc-NPh: M.p. 181 °C; ^{1}H NMR δ 7.42-7.07 (br.m,5H, Ph), 2.07, 1.62 (m,30H, adamantyl); ^{13}C NMR δ 151.4 (CO), 139.5, 128.5, 127.9, 127.2 (Ph), 82.5, 41.1, 36.1, 30.8 (adamantyl); IR (KBr) 1741, 1723 cm^{-1} (CO).

Compound (**3c**), Z(Adoc)NMe: oil; ^{1}H NMR δ 7.36 (s,5H,Ph), 5.21 (s,2H, CH_2O), 3.17 (s,3H,Me), 2.12, 1.65 (m,15H,adamantyl); ^{13}C NMR δ 154.0 (BzlOCO), 151.8 (CO Adoc), 135.6, 128.5, 128.2 (Ph), 82.7, 41.2, 36.1, 30.9 (adamantyl), 68.3 (CH_2O), 33.3 (Me); IR (film) 1793, 1752, 1724, 1697 cm^{-1}.

Compound (**3d**), Z(Adoc)-L-Ala-OEt: oil; ^{1}H NMR δ 7.36 (s,5H,Ph), 5.24 (s, 2H,CH_2O), 5.00 (q,J=7,1H,CH), 4.12 (q,J=7,2H,CH_2Me), 2.10, 1.63 (m,15H, adamantyl), 1.51 (d,J=7,3H,Me), 1.21 (t,J=7,3H,Me); ^{13}C NMR δ 170.7 (COEt), 153.6(CO),150.5 (CO), 135.3, 128.5, 128.3 (Ph), 83.6, 41.1, 36.1, 30.9 (adamantyl), 68.7 (CH_2O), 61.2 (CH_2Me), 54.4 (CH), 15.6 (Me), 14.1 (Me); IR (film) 1798, 1746, 1700 cm^{-1} (CO).

Compound (**3e**), Z(Adoc)-L-Val-OEt: oil; ^{1}H NMR δ 7.36 (s,5H,Ph), 5.25 (s,2H,OCH_2Ph), 4.55 (d,1H,CHN), 4.10 (q,2H,CH_2Me), 2.49 (m,1H,$CHMe_2$), 2.10, 1.64 (m,15H,adamantyl), 1.20 (t,3H,CH_3CH_2), 1.13 (d,3H,Me), 0.85 (d,3H,Me); ^{13}C NMR δ 170.1 (COOEt), 154.2 (BzlOCO), 150.9 (Adoc-CO), 135.4, 128.5, 128.3, 128.1 (Ph), 83.4, 41.1, 36.0, 30.9 (adamantyl), 68.7 (CH_2OCO), 63.8 (CHMe), 60.9 (CHN), 28.5 (CHMe$_2$), 22.2(Me), 18.8 (Me), 14.1 (CH_3CH_2); IR (film) 1796, 1747, 1704 cm^{-1} (CO).

Compound (**3f**), Boc(Adoc)Gly-OBzl: oil; ^{1}H NMR δ 7.34 (s,5H,Ph), 5.18 (s,2H,CH_2O), 4.37 (s,2H,CH_2N), 2.10, 1.64 (m,15H,adamantyl), 1.47 (s, 9H,Me_3); ^{13}C NMR δ 169.1 (COOBzl), 151.9 (CO), 151.2 (CO), 135.5, 128.5, 128.3 (Ph), 83.1, 41.1, 36.0, 30.9 (adamantyl), 82.9 (CMe_3), 66.8 (CH_2O), 47.4 (CH_2N), 28.0 (Me_3); IR (film) 1797, 1758, 1735, 1696 cm^{-1} (CO).

Compound (**3g**)=(**3h**), Ac(Adoc)Gly-OBzl: M.p. 44-44.5 °C; ^{1}H NMR δ 7.35 (s,5H,Ph), 5.17 (s,2H,CH_2O), 4.49 (s,2H,CH_2N), 2.54 (s,3H,Me), 2.15, 2.04, 1.63 (m,15H,adamantyl); ^{13}C NMR δ 172.7 (COMe), 168.8 (COOBzl), 151.6 (CO Adoc), 135.5, 128.5 (Ph), 83.8, 41.0, 35.9, 30.9 (adamantyl), 66.9 (CH_2O), 45.3 (CH_2N), 26.4 (Me); IR (KBr) 1753, 1741, 1704, cm^{-1} (CO).

Compound (**3i**), Ac(Boc)NPh[5]; ^{13}C NMR δ (DMSO-d_6) 171.9 ($COCH_3$), 152.1 (CO Boc), 138.8, 128.5, 128.2, 127.3 (Ph), 82.5 (CMe_3), 27.3 (Me_3), 26.2 (CH_3CO).

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