Reaction of Diethyl Azodicarboxylate with Ethers in the Presence of *N*-Hydroxyimides as Catalysts

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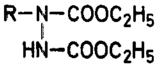
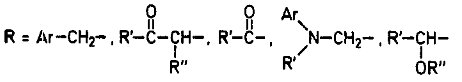
Diethyl azodicarboxylate (DEAD) reacts upon irradiation or on heating with numerous organic compounds such as alkylbenzenes, ketones, aldehydes, and tertiary amines to yield adducts of the type **1**, identical with the products obtained from the analogous reactions of DEAD in the presence of free-radical initiators[1]. The reactions of DEAD with alkyl ethers[2,3,4] under the influence of irradiation or free-radical initiators yield products of the same type **1**.

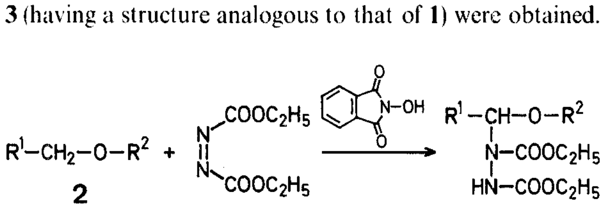


$R-N(COOC_2H_5)-NH-COOC_2H_5$ **1**



$R = Ar-CH_2-,\ R'-C(=O)-CH(R'')-,\ R'-C(=O)-,\ (Ar)(R')N-CH_2-,\ R'-CH(OR'')-$

In the course of our investigations[5] on the reaction of *N*-hydroxyimides with alcohols in the presence of DEAD and triphenylphosphine in tetrahydrofuran as solvent, we found that the hydroxy group of tertiary alcohols was not exchanged for the oximide group as in the case of primary and secondary alcohols. The sole reaction product formed, however in low yield, was a 1 : 1 adduct of DEAD and tetrahydrofuran. This result was surprising because known examples of the use of ethers as solvents in ionic reactions carried out in the presence of DEAD[6,7] suggested that ethers are inert reaction media. We concluded that the formation of the tetrahydrofuran-DEAD adduct in the above reaction must have resulted from a free-radical process initiated by *N*-hydroxyphthalimide. This observation prompted us to study in detail the reaction of DEAD with alicyclic and aliphatic ethers (**2**) in the presence of catalytic amounts (5 mol %) of *N*-hydroxyphthalimide. High yields of products **3** (having a structure analogous to that of **1**) were obtained.

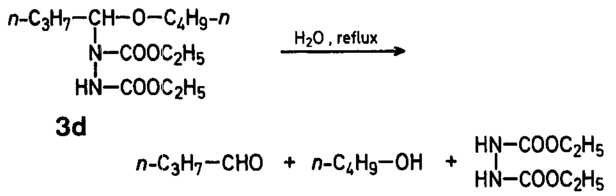


2 **3**

	R^1	R^2
a	$-CH_2-CH_2-CH_2-$	
b	$-CH_2-O-CH_2-CH_2-$	
c	$-O-CH_2-CH_2-CH_2-$	
d	n-C_3H_7	n-C_4H_9
e	CH_3	C_2H_5
f	C_6H_5	$C_6H_5-CH_2-$

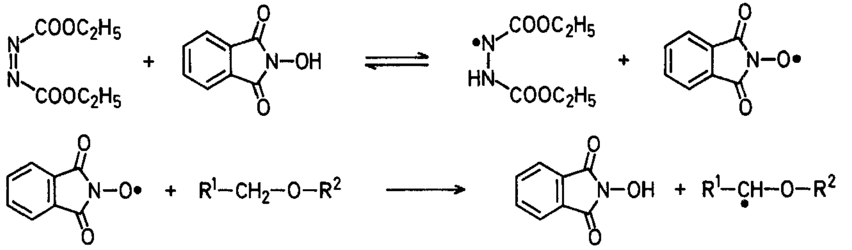
The reaction proceeds at elevated temperatures (up to 120°) in an excess of ethers serving as reactants and solvents in the presence of catalytic amounts of *N*-hydroxyphthalimide or *N*-hydroxysuccinimide. Compounds **3** are formed in nearly quantitative yield. The reaction proceeds also at higher temperatures without a catalyst but the reaction time is considerably longer (>24 h).

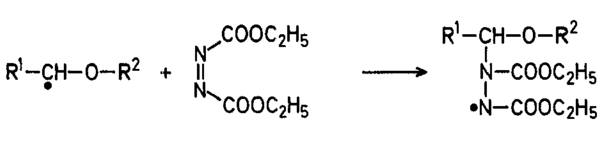
The structures of compounds **3a–f** were confirmed by I.R.- and ^{1}-N.M.R. spectrometry and by microanalyses. For all ethers **2**, only monosubstituted derivatives were obtained. In the case of the cyclic acetal 1,3-dioxane there are two possible non-equivalent substitution sites: positions 2 and 4; however, the only product is the 2-substituted compound which results from the higher electronegativity of position 2 in comparison with position 4. This is in agreement with the observations of Cookson[2] on the reaction of unsymmetric ethers with DEAD under irradiation. The hydrolysis of compounds of the type **3** to alcohols, carbonyl compounds, and diethyl hydrazine-1,2-dicarboxylate[2] further confirms the structure. We performed this reaction with **3d**.

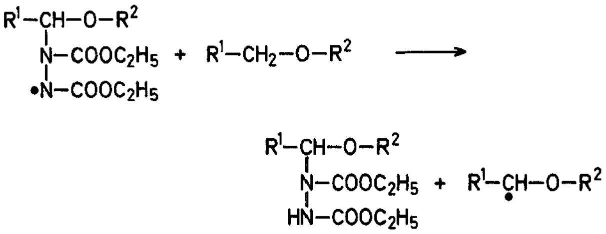


3d

The catalytic activity of the *N*-hydroxyimides in the reaction described may be attributed to the intermediate formation of nitroxyl radicals from the *N*-hydroxyimides and DEAD, and hydrogen abstraction from the alkyl ether by the nitroxyl; the 1-alkoxyalkyl radical thus formed then adds to DEAD to give a nitrogen radical which abstracts hydrogen from another ether molecule, thus giving rise to a radical chain reaction.







The radical character of this reaction was demonstrated by its failure to proceed in the presence of inhibitors such as hydroquinones and tetrachloro-*p*-benzoquinone. Also triphenylphosphine inhibits the reaction as can be seen from the low yields obtained in the presence of this reagent (5 mol %). Thus, the phthalimidoxylation reactions in tetrahydrofuran as solvent described by us previously never produced significant amounts of adducts of the type **3**.

Table. Reaction Conditions, Yields, Physical Properties, and Analytical Data of Compounds **3**

3	Reaction conditions	Yield [%]	b.p.[a]/torr or m.p. (Lit. data)	Molecular formula	I.R. (film)[c] ν_{NH}	$\nu_{C=O}$	^{1}H-N.M.R. (CCl_4)[d] δ [ppm]
a	70°, 9 h	96	b.p. 150–153°/0.5 (b.p. 110°/0.1)[3]	$C_{10}H_{18}N_2O_5$ (246.3)	3310	1750,1720	1.25 (t, 6H, $2CH_2{-}C\underline{H}_3$); 1.90 (m, 4H, $C{-}CH_2{-}CH_2{-}C$); 3.5–4.5 (m, 6H, $2\ C\underline{H}_2{-}CH_3$ and $CH_2{-}C\underline{H}_2{-}O$); 5.90 (m, 1H, CH—O); 7.25 (s, 1H, NH)
b	103°, 4 h	95	b.p. 145–147°/0.1	$C_{10}H_{18}N_2O_6$ (262.3)	3320	1750, 1710	1.35 (t, 6H, $2\ CH_2{-}C\underline{H}_3$); 3.4–4.6 (m, 10H, $2\ C\underline{H}_2{-}CH_3$, $O{-}C\underline{H}_2{-}CH$, $O{-}C\underline{H}_2{-}C\underline{H}_2{-}O$); 5.50 (m, 1H, CH—O); 7.32 (s, 1H, NH)
c	106°, 2 h	95	b.p. 141–143°/0.1	$C_{10}H_{18}H_2O_6$ (262.3)	3320	1750, 1720	1.35 (t, 6H, $2\ CH_2{-}C\underline{H}_3$); 1.6–2.2 (m, 2H, $O{-}CH_2{-}C\underline{H}_2{-}CH_2{-}O$); 3.4–4.5 (m, 8H, $2\ C\underline{H}_2{-}CH_3$, $O{-}C\underline{H}_2{-}CH_2{-}C\underline{H}_2{-}O$); 7.35 (s, 1H, O—CH—O); 8.10 (s, 1H, NH)
d	80°, 30 min	94	b.p. 128–131°/0.1	$C_{14}H_{28}N_2O_5$ (304.4)	3320	1755, 1720	0.95 (t, 6H, $2\ C{-}CH_2{-}C\underline{H}_3$); 1.30 (t, 6H, $2\ COOCH_2{-}C\underline{H}_3$); 1.3–1.7 (m, 8H, $2\ C{-}C\underline{H}_2{-}C\underline{H}_2{-}CH_3$); 3.1–3.6 (m, 2H, $O{-}C\underline{H}_2{-}CH_2$); 4.08 (q, 4H, $2\ COO{-}C\underline{H}_2{-}CH_3$); 5.1 (m, 1H, CH—O); 6.22 (s, 1H, NH)
e	80°, 12 h[e]	97	b.p. 120–122°/0.1	$C_{10}H_{20}N_2O_5$ (248.3)	3330	1750, 1720	1,20, 1.23, 1.30 (t, d, t, 12H, $O{-}CH_2{-}C\underline{H}_3$, $\underline{H}_3C{-}CH{-}O$, $2\ COOCH_2{-}C\underline{H}_3$); 3.35 (q, 2H, $O{-}C\underline{H}_2{-}CH_3$); 4.08 (q, 4H, $2\ COOC\underline{H}_2{-}CH_3$); 5.35 (m, 1H, CH—O); 6.85 (s, 1H, NH)
f	120°, 1.5 h	95	m.p. 88–89° (m.p. 81°)[4]	$C_{20}H_{24}N_2O_5$ (372.5)	3340	1750, 1690	1.21, 1.30 (2t, 6H, $2\ COOCH_2{-}C\underline{H}_3$); 4.05 (q, 4H, $2\ COOC\underline{H}_2{-}CH_3$); 4.70 ($AB_q$, 2H, $O{-}C\underline{H}_2{-}C_6H_5$); 5.95 (m, 1H, $C_6H_5{-}C\underline{H}{-}O$); 6.35 (s, 1H, NH); 7.15 (m, $10H_{arom}$)

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[a] Air bath temperature.

[b] All products gave satisfactory microanalyses: C, ±0.30; H, ±0.28; N, ±0.31.

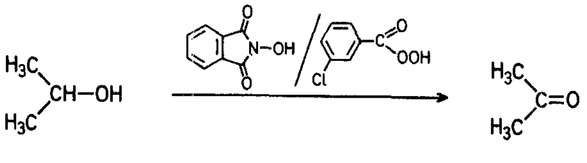
[c] I.R. spectra were recorded with a Unicam SP-200 spectrophotometer.

[d] ^{1}H-N.M.R. spectra were recorded on a Varian EM-360 spectrometer at 60 MHz.

[e] Sealed tube.

[f] KBr.

An additional proof for the intermediate conversion of *N*-hydroxyphthalimide into the nitroxyl in the presence of an oxidizing agent is the oxidation of isopropanol to acetone with 3-chlorobenzoperoxoic acid in the presence of catalytic amounts of *N*-hydroxyphthalimide. It is known from the literature[10] that the nitroxyl moiety efficiently initiates such reactions.



The reaction decribed in the present communication represents a convenient method for α-cleavage of ethers since hydrolysis of the adducts **3** gives nearly quantitative yields of alcohols and carbonyl compounds.

Diethyl 1-(2-Tetrahydrofuranyl)-hydrazine-1,2-dicarboxylate (3a); Typical Procedure:

Diethyl azodicarboxylate (348 mg, 2 mmol) and *N*-hydroxyphthalimide (15 mg, 0.1 mmol) are dissolved in tetrahydrofuran (10 ml) and the solution is refluxed for 9 h. Excess ether is evaporated under reduced pressure and the residue is distilled in vacuo; yield: 472.5 mg (96%); b.p. 150–153°/0.5 torr (air-bath temperature).

Butanal from 3d; Typical Hydrolysis Procedure:

Diethyl 1-(1-butoxybutyl)-hydrazine-1,2-dicarboxylate (**3d**; 608 mg, 2 mmol) is refluxed in water (2 ml) for 3 h. The mixture is then cooled and the product extracted with ether. The extract is dried with magnesium sulfate, the solvent evaporated, and the residue distilled; yield: 130 mg (90%); b.p. 118° (air bath temp.). [The butanal thus obtained was identified by G.L.C.]

Acetone from Isopropanol (cf. Ref.[10]):

3-Chlorobenzoperoxoic acid (2.59 g, 15 mmol) and *N*-hydroxyphthalimide (0.244 g, 1.5 mmol) are dissolved in isopropanol (20 ml). The solution is refluxed for 1 h, and then distilled. The distillate is treated with a methanolic solution of 2,4-dinitrophenylhydrazine, the precipitate isolated, and identified as acetone 2,4-dinitrophenylhydrazone; yield: 2.71 g (76% based on peroxoic acid).

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