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Tetrahedron Letters 45 (2004) 7455–7457

Tetrahedron Letters

ELSEVIER

Curtius rearrangement and Wolff homologation of functionalized peroxides

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Received 2 July 2004; revised 1 August 2004; accepted 9 August 2004
Available online 27 August 2004

Abstract—The Curtius and Wolff rearrangements of peroxide-containing alkanoyl azides and diazoketones provide an efficient entry to peroxy-substituted amines, isocyanates, carbamates, and peroxyalkanoates.

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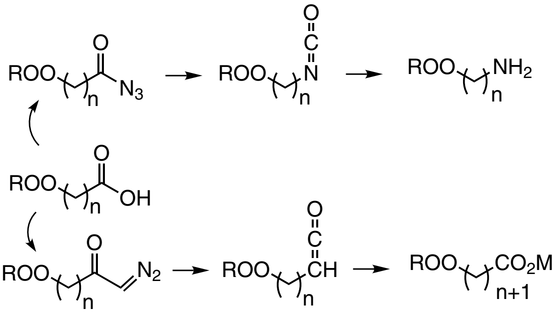
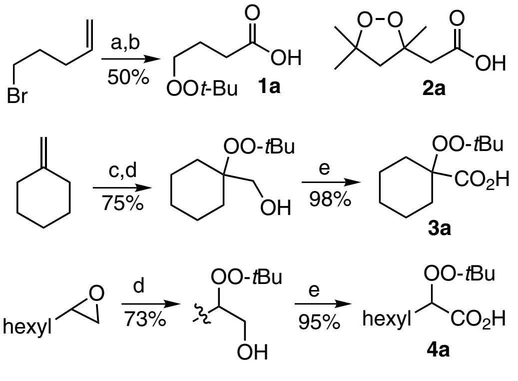
1. Introduction

Synthetic approaches to peroxides are typically constrained by the limited methodology available for introduction of the peroxide functional group.[1] For example, our recent investigations into redox-based enzyme inactivators[2] required preparation of 2-peroxyl and 3-peroxylalkylamines, poorly explored functional motifs.[3] We now report the successful Curtius rearrangement of peroxyalkanoyl azides as a method for synthesis of peroxy-substituted isocyanates, amines, and carbamates. In addition, we discovered that the corresponding Wolff rearrangement of peroxide-containing diazoketones provides a very effective method for homologation of peroxyalkanoates (Scheme 1).



Scheme 1. Curtius and Wolff rearrangements on peroxidic substrates.

Preparation of peroxyalkanoic acid substrates is illustrated in Scheme 2.[†] The synthesis of substrate **4a** includes the first example of acid-catalyzed intermolecular reaction of a hydroperoxide with a secondary epoxide, a reaction that was found to proceed with only moderate regioselectivity in favor of the more substituted peroxide.[4]



Scheme 2. Substrate preparation. Reagents and conditions: (a) t-BuO$_2$H, CsOH; (b) KMnO$_4$; (c) m-CPBA; (d) t-BuO$_2$H, BF$_3$OEt$_2$; (e) H$_2$CrO$_4$.

Keywords: Peroxide; Curtius; Wolff; Peroxyalkanoate.

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[†] All new compounds were purified to homogeneity and characterized by ^{1}H, ^{13}C, IR, and HRMS, except for **1d**–**4d**, where no molecular ions were observed.

0040-4039/$ - see front matter
doi:10.1016/j.tetlet.2004.08.059

2. Curtius rearrangements

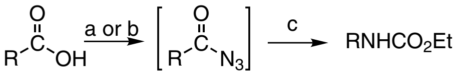
Conversion of the peroxyalkanoic acids to acyl azides was readily achieved via the mixed anhydrides, with the exception of the hindered acid **3a**, which required activation as the acid chloride (Table 1).[5] The azides were stable to extractive isolation but decomposed upon attempted purification. Heating the crude azides with ethanol in refluxing benzene directly furnished the ethyl carbamates **1b**, **2b**, and **4b** as stable products. In the case of the hindered azide derived from **3a**, thermolysis resulted in decomposition with loss of the peroxide functional group.[6]

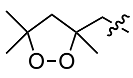
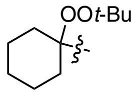
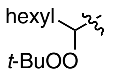
We also briefly investigated aprotic thermolysis of an azide as an approach to a peroxide-containing isocyanate. Refluxing the acyl azide derived from **2a** in dry benzene furnished a dioxolane isocyanate, which was not isolated but which could be observed by IR (Scheme 3). Hydrolysis of the isocyanate in aqueous acid furnished the aminomethyl dioxolane **5**, which underwent coupling with CBZ-Phe to furnish a peroxide-containing amino acid **6**.

3. Wolff rearrangement

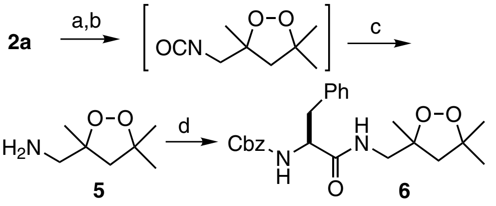
The success of the Curtius rearrangements described above led us to consider the potential of the Wolff rearrangement for preparation of peroxyalkanoates, a functional motif found in a number of marine natural products.[7] As shown in Table 2, the peroxyalkanoic acids were easily converted, via the mixed anhydrides or the acid chlorides, to isolable diazomethyl ketones. Reaction of diazoketones **1c** or **2c** with silver benzoate and triethylamine in methanol furnished the homologated peroxyalkanoates **1d** or **2d** in excellent yield.[8]

Table 1. Curtius rearrangement of peroxylalkanoyl azides



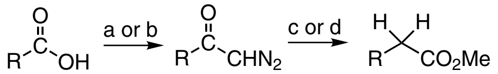
R		Method	Carbamate	Yield (%)
t-BuOO(CH$_2$)$_3$-	**1a**	a	**1b**	47
	**2a**	a	**2b**	55
	**3a**	b	—	—
	**4a**	a	**4b**	60

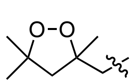
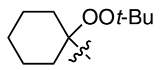
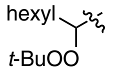
(a) EtOC(O)Cl then NaN$_3$; (b) (ClCO)$_2$ then NaN$_3$; (c) EtOH, benzene, reflux.



Scheme 3. Synthesis of dioxolane isocyanate and aminomethyl dioxolane. Reagents and conditions: (a) EtOC(O)Cl then NaN$_3$; (b) C$_6$H$_6$, reflux; (c) aq HCl; (d) CBZ-Phe, DCC.

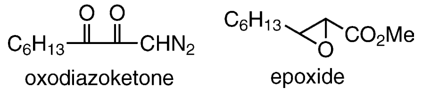
Table 2. Homologation via diazoketones



	R		Diazoketone	Ester
1a	*t*-BuOO(CH$_2$)$_3$	a	**1c** (78%)	**1d** (99%)
2a		a	**2c** (82%)	**2d** (99%)
3a		b	**3c** (75%)	**3d** (75%)
4a		a	**4c** (70%)	**4d** (83%)

(a) EtOC(O)Cl then CH$_2$N$_2$; (b) ClCOCOCl then CH$_2$N$_2$; (c) AgOBz (0.1 equiv), Et$_3$N, MeOH; (d) hν, MeOH, HOAc.

Application of these conditions to substrate **4c** resulted in a poor yield of homologated product, accompanied by significant amounts of the oxodiazoketone, apparently derived from base-promoted decomposition of the starting material (Eq. 1).[9] Photochemical Wolff rearrangement (254 nm, methanol) furnished a much better yield of the homologated peroxyalkanoate **4d**, accompanied by small amounts of 2,3-epoxynonanoate, which presumably arises via intramolecular attack of a developing ester enolate on the peroxide. Performing the photochemical rearrangement in the presence of a trace amount of acetic acid resulted in an improved yield of peroxyalkanoate. The tertiary peroxide substrate **3c**, which failed to give any homologation product in the presence of AgOBz/Et$_3$N, underwent photochemical rearrangement to afford peroxyalkanoate **3d**.



(1)

In conclusion, we have demonstrated the ability to employ the Curtius and Wolff rearrangements for synthesis of peroxylamines or homologated peroxyalkanoates. The ability to homologate 2- and 3-peroxyalkanoic acids holds particular promise for synthesis of peroxide natural products while the ability to perform the Curtius rearrangement opens new possibilities for the introduction of natural or unnatural peroxide-containing groups onto polymers and biomolecules.

4. Caution

While we experienced no particular problems, any research involving peroxides, azides, and similar functional groups should be conducted with appropriate precautions against spontaneous exothermic decomposition.

Supplementary data

Experimental procedures and spectral listings for new compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.08.059.

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