Notes

Thermal Rearrangement of α-(Aryloxy)methylacrylic Acids: A Facile Synthesis of 3-Methylcoumarins†

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Polyethylene glycol (PEG) has gained prominence as a solvent of choice in recent years due to its unique structural features and practical usage.[1-4] Earlier work from our laboratory has shown that there is a considerable rate enhancement (by a factor of 2–2.5) of the rearrangement of aryl propargyl ethers in PEG-200 as compared to that in *N,N*-diethylaniline.[5] Also, a detailed study of the rearrangement of 1,4-bis(aryloxy)-2-butynes in PEG-200 indicated a selective transformation of these ethers to benzofuro[3,2-*b*]- or benzofuro[2,3-*b*]benzofuran by varying the temperature of the reaction.[6]

In this paper, we wish to report the use of PEG-200 as a solvent for aromatic Claisen rearrangement which incidentally provided a facile synthesis of 3-methylcoumarins (**4**).

The thermal transformation of α-(aryloxy)methylacrylic acids **1** to the spiro dimer **2** in refluxing *o*-DClB has been reported by us.[7] In total contrast to this, heating the acrylic acids **1** in PEG-200 at 220 °C for 30 min afforded exclusively the 3-methylcoumarins **4** in moderate to high yields (Scheme I) (Table I).

The above rearrangement was investigated in a number of other solvents, viz., *o*-DClB, *N,N*-DEA, ethylene glycol, diethylene glycol, hexamethylphosphoric triamide, *N*-methyl-2-pyrrolidone.

Though diethylene glycol (bp 244–45 °C) and ethylene glycol (bp 194–95 °C), which possesses chemical and structural properties similar to that of PEG-200, have been employed for ortho-Claisen rearrangements,[8] our present work has brought our the subtle difference between EG/DEG and PEG as solvents in these rearrangement reactions. Thus it was observed that PEG-200 was not only effective in bringing about the rearrangement to the intermediate 3-methylenecoumarin **3** but also a clean isomerization to give **4**, whereas under identical conditions in EG or DEG relatively less isomerization and formation of **4** have been noticed. To corroborate this observation, the reaction was carried out in ethylene glycol, diethylene glycol, and PEG-200, under identical conditions. The results of this study are summarized in Table II.

It was obvious from the table that under identical conditions, formation of 3-methylcoumarin is maximum in PEG-200 as compared to ethylene glycol or diethylene glycol. Thus PEG is not only effective in bringing about a modest rate enhancement, but its increased basic nature is helpful in effecting the isomerization also.

Scheme I

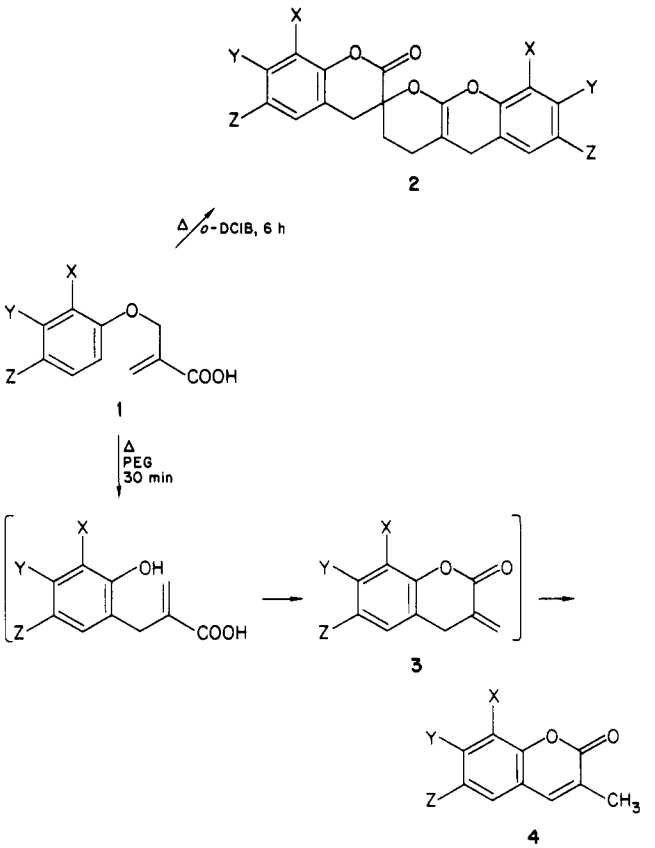

Table I. Preparation of 3-Methylcoumarins[a] in PEG-200

X	Y	Z	yield[b]	mp, °C
H	H	H	86	69–70
H	H	CH_3	91	114–116
H	H	Cl	95	158–159
H	CH=CHCH=CH		96	157–58
H	H	OCH_3	80	100–102
CH_3	H	H	88	48–50
CHO	H	H	82	85–88
CH=CHCH=CH		H	85	108–110
H	H	CHO	72	165–166
H	H	$COCH_3$	73	136–138
H	H	NO_2	50	147–148

[a] All new compounds gave satisfactory analytical and spectral data. [b] Based on isolated yields.

Table II. Rearrangement of 1 in PEG-200, Diethylene Glycol, and Ethylene Glycol

	3-methylenecoumarin:3-methylcoumarin (3:4)		
solvent	160 °C, 2 h	180 °C, 2 h	220 °C, 30
ethylene glycol	3:1	1:1	
diethylene glycol	2:1	1:1	1:2
PEG-200	1:2	1:6	0:1

† Dedicated to Prof. C. L. Stevens, Wayne State University, Detroit, MI, on the eve of his 60th birthday.

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The formation of 3-methylcoumarin 4 from the acid 1 has been observed only under the influence of a base.[9] Thermal rearrangement of acrylic acid 1 in *o*-DClB in the presence of a catalytic amount of PTS resulted only in the formation of dimer 2. In HMPA and *N*-methyl-2-pyrrolidone, considerable cleavage of the acid 1 to the corresponding phenol was observed apart from the formation of the 3-methylcoumarins in very poor yields. In DEA, apart from the formation of coumarin 4 a small amount of dimer 2 was also obtained.

The several features associated with PEG-200, viz., complete miscibility with water and consequently easy workup of the reaction mixture, high boiling point, polar nature, higher selectivity, nontoxicity, and low cost particularly, prompted us to investigate its utility in the field of Claisen and Cope rearrangements.

In our experience, we find PEG to be a superior solvent for Claisen rearrangement of α-(aryloxy)methylacrylic acids affording 3-methylcoumarins in high yields.

Experimental Section

Melting points (uncorrected) were taken with Toshnival Capillary apparatus. ^{1}H NMR spectra were recorded with Me_4Si as an internal standard in $CDCl_3$. Commercial SD'S sample of Polyethylene glycol-200 was used. Diethylene glycol and ethylene glycol were flame distilled before use.

General Procedure for Preparation of 3-Methylcoumarins in Polyethylene Glycol. A solution of 1 (200 mg 0.001 mol) in 10 mL of polyethylene glycol-200 was heated for exactly 30 min at a temperature of 220 °C under argon atmosphere. The reaction mixture was cooled and poured into water. The 3-methylcoumarins 4 separated out in most cases as a good solid in high yields and were crystallized from benzene–hexane (Table I). Table I lists the melting points of the various substituted 3-methylcoumarins: IR ($CHCl_3$) ν_{max} C=O at 1700 cm^{-1}; NMR ($CDCl_3$) values at 2.2 (s, 3 H), 7.4–7.6 (m, Ar H), 7.3 (s, 1 H, Ar C=).

The reactions in diethylene glycol and ethylene glycol were performed by following the same above procedure (Table II).

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Registry No. 1 (X = Y = Z = H), 57295-21-3; 1 (X = Y = H, Z = CH_3), 56634-11-8; 1 (X = Y = H, Z = Cl), 57295-22-4; 1 (X = H, Y,Z = CH=CHCH=CH), 57295-23-5; 1 (X = Y = H, Z = OCH_3), 95532-63-1; 1 (X = CH_3, Y = Z = H), 95532-64-2; 1 (X = CHO, Y = Z = H), 95532-65-3; 1 (X,Y = CH=CHCH=CH, Z = H), 95532-66-4; 1 (X = Y = H, Z = CHO), 95532-67-5; 1 (X = Y = H, Z = $COCH_3$), 95532-68-6; 1 (X = Y = H, Z = NO_2), 95532-69-7; 3 (X = Y = Z = H), 56783-44-9; 4 (X = Y = Z = H), 2445-82-1; 4 (X = Y = H, Z = CH_3), 57295-24-6; 4 (X = Y = H, Z = Cl), 57295-25-7; 4 (X = H, Y,Z = CH=CHCH=CH), 86818-99-7; 4 (X = Y = H, Z = OCH_3), 62399-35-3; 4 (X = CH_3, Y = Z = H), 95532-70-0; 4 (X = CHO, Y = Z = H), 95532-71-1; 4 (X,Y = CH=CHCH=CH, Z = H), 21315-40-2; 4 (X = Y = H, Z = CHO), 95532-72-2; 4 (X = Y = H, Z = $COCH_3$), 95532-73-3; 4 (X = Y = H, Z = NO_2), 95532-74-4; polyethylene glycol, 25322-68-3; ethylene glycol, 107-21-1; diethylene glycol, 111-46-6.

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Facile One-Step Synthesis of Phenyl-*tert*-butylnitrone (PBN) and Its Derivatives

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In recent years, the technique of spin trapping has provided detailed information on radical processes.[1] This is especially true for radical reactions occurring in the biological milieu.[2] Of the spin traps which have been utilized, phenyl-*tert*-butylnitrone (PBN) and its derivatives are some of the most important.[1-3] Indeed, derivatives of PBN that are water-soluble,[4] lipid-soluble,[5] and polymer-bound[6] have been prepared and shown to be effective trapping agents.

Currently, two methods for the preparation of these types of spin traps are known. The first involves conversion of an aldehyde into a *tert*-butyl imine followed by oxidation to the oxazirane and final rearrangement to the nitrone.[7] Overall yields are generally low and the oxidation step calls for 90% H_2O_2 although 30% may be used with a decreased yield.[7] The second method is direct addition of *tert*-butylhydroxylamine to the corresponding aldehyde.[5] This procedure results in relatively high yields. However, the hydroxylamine has typically been prepared by reduction of the nitro compound with Al/Hg amalgam[8] or activated zinc[9] and then is purified prior to condensation with the aldehyde. We now detail a simplified, one-step preparation of PBN and its derivatives.

An early report by Wiemann and Glacet on the synthesis of diaryl nitrones prompted us to investigate a similar procedure for arylalkylnitrones.[10] In this procedure, the hydroxylamine is prepared from the nitro compound in situ via reduction with metallic zinc. By modification of this procedure, high yields of nitrone have been achieved in a single step. The results for several nitrones are shown in Table I. Particularly useful is the high yield of the lipid-soluble dodecyloxy derivative.

The general procedure is to cool a mixture of 1 equiv of the appropriate aldehyde, 2 equiv of 2-methyl-2-nitropropane, and 3 equiv of activated zinc dust in 95% EtOH to 10–15 °C. Glacial acetic acid is then added dropwise while maintaining the sample temperature below 15 °C. After being stored in the refrigerator (~6 °C) for 24–48 h, the sample is filtered and the solvent removed. The NMR analysis of the crude nitrone indicates >95% purity with essentially no aldehyde contamination. A single recrystallization yields suitably pure nitrone (mp range <3 °C and no residual EPR signal).

All of the variables pertaining to this procedure have not been investigated through the best solvent appears to be

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