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$AlCl_3$-DMA REAGENT IN THE REGIOSELECTIVE SOLVENT FREE FRIEDEL-CRAFTS ACYLATION REACTION OF BENZODIOXIN DERIVATIVES

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Abstract: A general method for the regioselective solvent free Friedel–Crafts acylation of 2–substituted–1,4–benzodioxin derivatives in excellent yields employing the $AlCl_3$–DMA reagent with acyl halides or anhydrides as acylating agents is described. The acylation of 2–substituted–1,4–benzodioxin derivatives provides the 6–acyl compound as the major product. However, the saturated analogs affords the 7–acyl regioisomer as the main compound.

The Friedel-Crafts acylation is a synthetic method of wide application in organic synthesis. Commonly, acyl halides or anhydrides in the presence of aluminum chloride ($AlCl_3$) are used as reagent, but these classical conditions are not suitable for certain aromatic substrates. It is considered that when the aromatic substrate bears electron–donating substituents possessing lone pairs available for complexation, the Lewis acid complexes more extensively to the substrate than to the electrophile-generating species. The 2,3-dihydro-1,4-benzodioxin ring is present in many natural and synthetic products. Derivatives of this nucleus bearing an acyl group in position 6 or 7 are key intermediates in the preparation of therapeutically valuable benzodioxin compounds.[1] Hitherto, procedures allowing regioselective functionalization on the aromatic ring of these substrate have been circumscribed to the use of $AlCl_3$-carbon disulfide with acyl halides.[2] Therefore, the development of efficient regioselective methods which could produce these compounds are of continuous interest.

A previous paper demonstrated that the combination of $AlCl_3$ with an organic donor ligand is an excellent reagent for the acylation reaction of benzodioxin derivatives, which is carried out in the absence of added solvent.[3] As part of our continuing effort to broaden the scope of this methodology we have investigated the used of other donor ligands in combination with a Lewis acid. The present work reports the results obtained with the use of $AlCl_3$ in conjunction with N,N–dimethylacetamide (DMA) for the regioselective acylation of 2-substituted-1,4-benzodioxin derivatives with acyl halides and anhydrides as acylating reagents. The $AlCl_3$ is partially complexed to the organic ligand under the experimental conditions employed, modulating its Lewis acid acidity, consequently the $AlCl_3$ complexes to a lesser extend to the aromatic substrate allowing the reaction to take place. Scheme 1 represents the different saturated and unsaturated 2–substituted–1,4–benzodioxin derivatives employed in this study.

The reaction takes place readily at room temperature affording the monoacylated product in good to excellent yields, regardless the nature of the acyl chloride or anhydride employed.[4] Table 1 reports the yields of analytically pure material and the isomeric ratio of the 6 and 7 acyl products.

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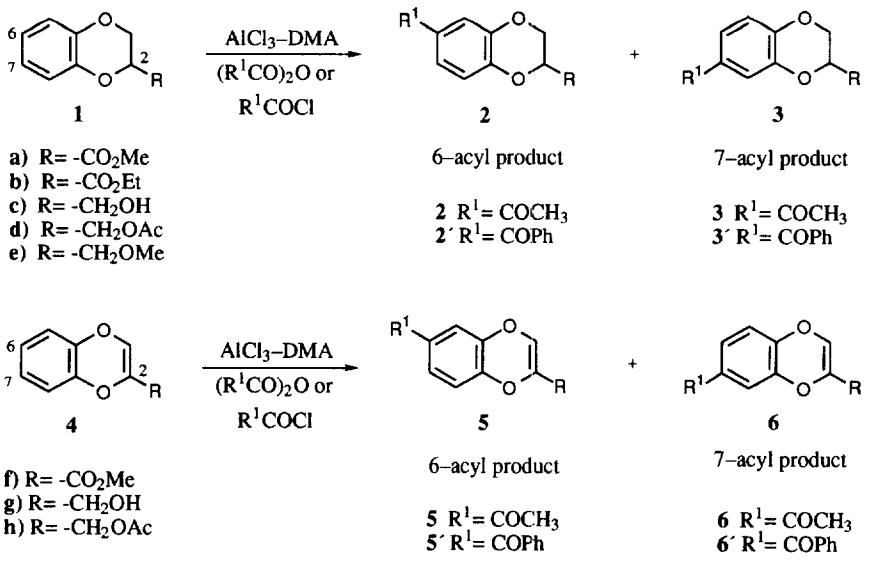


Scheme 1

Both 6– and 7–position of the aromatic ring of the substrate are activated towards the electrophilic substitution reaction; however, the Friedel-Crafts acylation of the saturated 1,4-benzodioxin derivatives **1 a–e** resulted in the formation of the C-7 monoacylated product as the major isomer, in a ratio that depends on the nature of the R group. In contrast , the unsaturated analog **4 f** afforded the C-6 monoacylated product as the main compound. Decomposition was observed with the alkyloxy derivatives **4 g** and **4 h**. These results can be rationalized in terms of the higher nucleophilicity of the heterosubstituted double bond in these substrates, which makes them more susceptible to reaction involving a cation intermediate.[5]

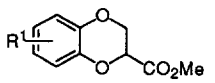
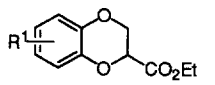
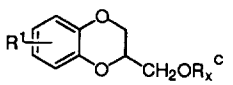
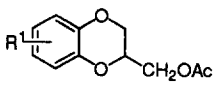
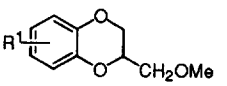
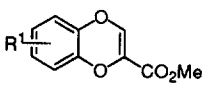
The results obtained with the different acylating reagents demonstrate that the nature of the reacting electrophile has almost no influence on the isomeric distribution. It is worth mentioning that the aromatic acylation of substrate **1 c** also affords the corresponding ester derivative. Attempts to reduce the amount of acyl chloride or anhydride to avoid the esterification only afforded lower yields of acylated ester. This result suggests that the ester formation readily takes place before the electrophilic substitution reaction.

The behavior of the AlCl3–DMA reagent in these reactions appears to be parallel to that of AlCl3-DMSO and AlCl3-DMF previously reported,[3] providing good yields for the saturated 2,3–dihydro–1,4–benzodioxin derivatives bearing electron–donating or withdrawing substituent at C–2. In the case of the benzodioxin derivatives **4 f–h**, the outcome of the reaction proved to be dependent on the nature of the R group. Nevertheless, the acylated derivatives of substrates **4 g** and **4 h** can be obtained by functional group interconvertion from the acylated products of **4 f**.

In conclusion, the AlCl3-DMA is an excellent reagent for the regioselective acylation of 2-substituted-1,4-benzodioxin derivatives and provides a new valuable alternative for this class of aromatic substrates. The combination of

$AlCl_3$ with donor ligands appears to be an efficient reagent for the Friedel-Crafts acylation of substrates that do not react under classical conditions and provides a highly promising synthetic method in light of some recent examples which do not require the use of solvents.[6]

Table 1

Substrate R	Product	R^1	Acylating reagent	Yield (%)[a]	Isomeric ratio product[b]
CO_2Me (a)		$COCH_3$	$(CH_3CO)_2O$	94	**2a:3a** = 15:85
		$COCH_3$	CH_3COCl	97	**2a:3a** = 15:85
		COPh	PhCOCl	88	**2´a:3´a** = 15:85
CO_2Et (b)		$COCH_3$	$(CH_3CO)_2O$	73	**2b:3b** = 20:80
		$COCH_3$	CH_3COCl	79	**2b:3b** = 20:80
		COPh	PhCOCl	69	**2´b:3´b** = 20:80
CH_2OH (c)		$COCH_3$	$(CH_3CO)_2O$	86	**2d:3d** = 35:65
		$COCH_3$	CH_3COCl	85	**2d:3d** = 35:65
		COPh	PhCOCl	64	**2´i:3´i** = 35:65
CH_2OAc (d)		$COCH_3$	$(CH_3CO)_2O$	89	**2d:3d** = 35:65
		$COCH_3$	CH_3COCl	99	**2d:3d** = 35:65
		COPh	PhCOCl	97	**2´d:3´d** = 35:65
CH_2OMe (e)		$COCH_3$	$(CH_3CO)_2O$	89	**2e:3e** = 30:70
		$COCH_3$	CH_3COCl	80	**2e:3e** = 30:70
		COPh	PhCOCl	98	**2´e:3´e** = 30:70
CO_2Me (f)		$COCH_3$	$(CH_3CO)_2O$	88	**5f:6f** = 90:10
		$COCH_3$	CH_3COCl	95	**5f:6f** = 90:10
		COPh	PhCOCl	80	**5´f:6´f** = 90:10

[a]Overall yield of the isolated mixture of acylated isomers. [b]Isomer ratio calculated from the ^1H NMR spectra. [c]Rx will be $COCH_3$ or COPh according to the acylating reagent employed.

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References and Notes

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3 E. G. Mata and A. G. Suárez, *Synth. Commun.*, **1997**, *27*, 1291.
4 **General Procedure**.– The reactions were carried out under atmosphere of nitrogen. The appropriate amount of DMA (1.2 mmoles, 110 μL) was slowly added to anhydrous aluminum chloride (3 mmoles, 400 mg). The mixture was stirred at room temperature for 30 minutes and the substrate (0.3 mmoles) was added. After 15 minutes, the acid anhydride or chloride (0.36 mmoles) was added in one portion. The reaction mixture was stirred for 12 hours at room temperature, hydrolyzed with ice and extracted 3 times with dichloromethane. The combined organic extract was neutralized with saturated $NaHCO_3$ solution, dried over anhydrous $MgSO_4$, and evaporated *in vacuo*. The acylated products were purified (but not separated) by flash chromatography or by filtration through a short pad of silica gel. All compounds gave satisfactory spectral and analytical data. Spectral data of new compounds:

7-Benzoyl-2-benzoxymethyl-2,3-dihydro-1,4-benzodioxin (3'i) colorless oil. IR (KBr): 1725 (C=O, ester), 1660 (C=O, ketone), 1500, 1451, 1432, 1297, 1270, 1105 cm^{-1}. ^1H NMR ($CDCl_3$) δ 4.15-4.35 (m, 1H, H-2), 4.40-4.70 (m, 4H, H-3 and CH_2O), 6.96 (d, $J_{5,6}$=8.2 Hz, 1H, H-5), 7.35-7.75 (m, 8H, H-6, H-8, $H_{arom.}$), 7.77 (d, 2H, $H_{arom.}$), 8.04 (d, 2H, $H_{arom.}$). ^{13}C NMR ($CDCl_3$) δ 195.0 (PhCO), 165.9 (CO_2Ph), 146.8, 142.2, 137.8, 131.2, 129.2 (C-7, C-9, C-10, C-1', C-1"), 131.8, 131.2, 129.5, 128.3, 128.0, 124.3, 119.7, 116.8 (C-5, C-6, C-8, $CH_{arom.}$), 70.8 (C-2), 65.3, 62.6 (C-3, CH_2O). MS m/z (relative intensity) 374 (9, M^+), 252 (50), 175 (63), 105 (100), 77 (60). Anal. Calcd for $C_{23}H_{18}O_5$: C, 73.79; H, 4.85. Found: C, 73.50; H, 4.94.

7-Acetyl-2-methoxymethyl–2,3-dihydro-1,4-benzodioxin (3e) colorless oil. IR (KBr): 1680 (C=O, ketone), 1615, 1590, 1510, 1437, 1365, 1300, 1200 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.52 (s, 3H, CH_3CO), 3.43 (s, 3H, CH_3O), 3.60-3.65 (m, 2H, H-3), 4.05-4.15 (m, 1H, H-2), 4.75-4.95 (m, 2H, CH_2O), 6.90 (d, $J_{5,6}$=8.2 Hz, 1H, H-5), 7.46–7.54 (m, 2H, H-6 and H-8). ^{13}C NMR ($CDCl_3$) δ 196.3 (CH_3CO), 147.4, 142.7, 131.2 (C-7, C-9, C-10), 122.5, 117.9, 1176.8 (C-5, C-6, C-8), 71.8 (C-2), 70.9, 65.3, (C-3, CH_2O), 59.4 (CH_3O), 26.1 (CH_3CO). MS m/z (relative intensity) 222 (53, M^+), 207 (100), 177 (22), 149 (8). Anal. Calcd for $C_{12}H_{14}O_4$: C, 68.85; H, 6.35. Found: C, 64.35; H, 6.34.

7-Benzoyl-2-methoxymethyl-2,3-dihydro-1,4-benzodioxin (3'e) colorless oil. IR (KBr): 1655 (C=O, ketone), 1605, 1585, 1501, 1455, 1435, 1290, 1207, 1120 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.42 (s, 3H, CH_3O), 3.62-3.68 (m, 2H, H-3), 4.09-4.19 (m, 1H, H-2), 4.31-4.40 (m, 2H, CH_2O), 6.95 (d, $J_{5,6}$=8.2 Hz, 1H, H-5), 7.36-7.56 (m, 5H, H-6, H-8, $H_{arom.}$), 7.72-7.77 (m, 2H, $H_{arom.}$). ^{13}C NMR ($CDCl_3$) δ 195.1 (PhCO), 147.1, 142.5, 137.9, 130.8 (C-7, C-9, C-10, C-1'), 131.8, 129.6, 128.0, 124.2, 119.8, 116.8 (C-5, C-6, C-8, $CH_{arom.}$), 71.8 (C–2), 70.9, 65.7 (C-3, CH_2O), 59.4 (CH_3O). MS m/z (relative intensity) 284 (73, M^+), 207 (100), 175 (15), 105 (43). Anal. Calcd for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67. Found: C, 71.65; H, 5.67.

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