The Chemistry of Acylals. Part II. Formation of Nitriles by Treatment of Acylals with Trimethylsilyl Azide in The Presence of a Lewis Acid

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Abstract: When acylals from aliphatic and aromatic aldehydes are treated with trimethylsilyl azide in the presence of titanium(IV) chloride, the latter group of compounds is converted to the corresponding nitriles in good to excellent yields. By-products were not formed. © 1998 Elsevier Science Ltd. All rights reserved.
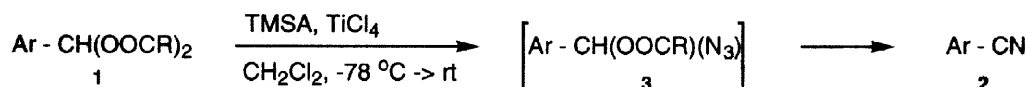
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Acylals, or *gem*-bis(acyloxy)-substituted compounds, are ambident substrates containing two types of reactive carbon centres, the carbon atom of a protected aldehyde function and the carbonyl group in the ester moieties. In general carbon nucleophiles will predominantly attack the former centre and displace one of the acyloxy groups [3-9], affording substitution products in excellent yields in the best cases [8,9]. Oxygen and nitrogen nucleophiles, on the other hand, attack almost exclusively one of the acyloxy groups, giving the corresponding aldehydes and acid derivatives as the primary products [10-13]. It was, therefore, doubtful that acylals would undergo substitution reactions when treated with sodium azide. Indeed, when reactions were carried out under standard conditions [14], phase-transfer catalysis [15,16], ultrasound irradiation [17] and Pd(0) catalysis [18], barely any reaction took place, but when benzylidene diacetate (**1a**) was exposed to a large excess of NaN_3 in refluxing benzene a 79% yield of diazidophenylmethane [1] [19] was obtained.

$$Ph\text{-}CH(OAc)_2 \xrightarrow[\text{Benzene, 80 °C, 10 hrs}]{NaN_3 \text{ (4 equiv.)}} Ph\text{-}CH(N_3)_2$$

1a   79%
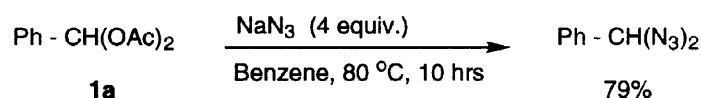
[1] **Proved to decompose violently when exposed to elevated temperature; see also ref. [14].**

Formation of the diazide was encouraging and suggested that other acylals could undergo azide displacement as well, provided the right reaction conditions could be worked out. With acetals a similar situation was resolved by applying trimethylsilyl azide (TMSA) and a Lewis acid (tin(IV) chloride) at ambient temperature, which gave the corresponding 1-alkoxy-1-azidoalkanes, albeit in moderate yields [20, 21]. We, therefore, exposed **1a** to TMSA under these conditions. This compound was indeed partly consumed, but the isolated product was benzonitrile (**2a**) and not the corresponding azido(phenyl)methyl acetate (**3a**). Application of other Lewis acids did not facilitate the isolation of **3a**, but the yield of **2a** turned out to be Lewis-acid sensitive and peaked at 73%

$$\text{Ar - CH(OOCR)}_2 \quad \xrightarrow[\text{CH}_2\text{Cl}_2, \text{-78 }^\circ\text{C -> rt}]{\text{TMSA, TiCl}_4} \quad \left[\text{Ar - CH(OOCR)(N}_3)\right] \quad \longrightarrow \quad \text{Ar - CN}$$

$$\quad\quad 1 \quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad 3 \quad\quad\quad\quad\quad\quad\quad 2$$

when titanium(IV) chloride was used. A range of acylals from aliphatic and aromatic aldehydes were therefore reacted with TMSA in the presence of TiCl4 at room temperature using the following *general procedure*: A dry round-bottomed flask, filled with nitrogen, was charged with the acylal (3 - 6 mmol) followed by the addition of dry dichloromethane (5 mL) and TMSA (1.2 equiv.). The reaction flask was immersed in a dry-ice cooling bath and TiCl4 (1.2 equiv.) was added dropwise with stirring. When the addition was complete, the bath was removed and the mixture was stirred at room temperature for 2 hours. Water (50 mL) was then added and the product was extracted with diethyl ether (3 x 30 mL). The combined extracts were washed with water (2 x 40 mL), dried (MgSO4), filtered and concentrated under vacuum. The crude product was analyzed and purified as required.

When reactions were performed as described, two reactivity patterns emerged. Firstly, all *the aromatic acylals were readily consumed* and gave the corresponding benzonitriles (**2**) as the only products in good to excellent yields (Table) whereas *the aliphatic analogues barely reacted*. This clear-cut difference between the two groups of acylals is somewhat surprising, but the aryl groups apparently make the protected aldehyde carbon atom electrophilic enough to react with the azide ion. Secondly, when the aromatic acylals react the outcome is hardly influenced by the substituent attached to the phenyl ring (Table). These results contrast with those obtained by reacting *aldehydes* with TMSA/ZnCl2 at rt; for instance, under these conditions **2b** is obtained in 82% yield from 4-methylbenzaldehyde whereas only traces of **2e** are formed from 4-nitrobenzaldehyde [15].

Furthermore, the aldehydes generally afford both *gem*-diazides (potential danger, see footnote) and 1*H*-tetrazoles as by-products, some times even in considerable amounts [18].

Table

Benzonitriles (2) from Reactions of Aromatic Acylals (1) with Timethylsilyl Azide (TMSA) in the Presence of Titanium(IV) Chloride.

Acylal	Ar	R	Product	Isolated yield/%
1a	C_6H_5	Me	**2a**	73
1b	4-Me-C_6H_5	Me	**2b**	95
1c	4-MeO-C_6H_5	Me	**2c**	82
1d	4-Cl-C_6H_5	Me	**2d**	97
1e	4-NO_2-C_6H_5	Me	**2e**	70
1f	C_6H_5	Pentyl	**2a**	90

Since our reaction is clean and acylals from aromatic aldehydes are easily available in good yields in reactions easily carried out on a large scale [8], the method reported here is a good and attractive alternative benzonitrile synthesis.

The mechanism for the reaction has not been investigated in any detail, but since the aldehydes corresponding to **1** can be ruled out as intermediates (**2e** is formed) [19], relevant literature [22, 23] supports the stepwise route outlined below.
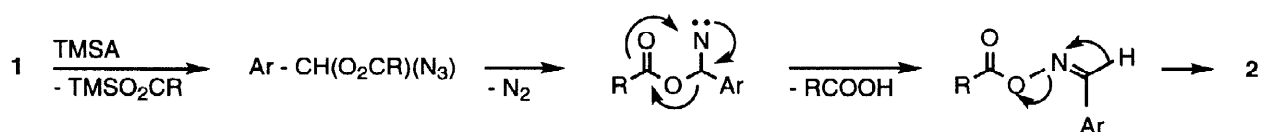
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