Synlett T. F. Mabasa et al. Letter

Acetic Anhydride–Acetic Acid as a New Dehydrating Agent of Aldoximes for the Preparation of Nitriles: Preparation of 2-Cyanoglycals

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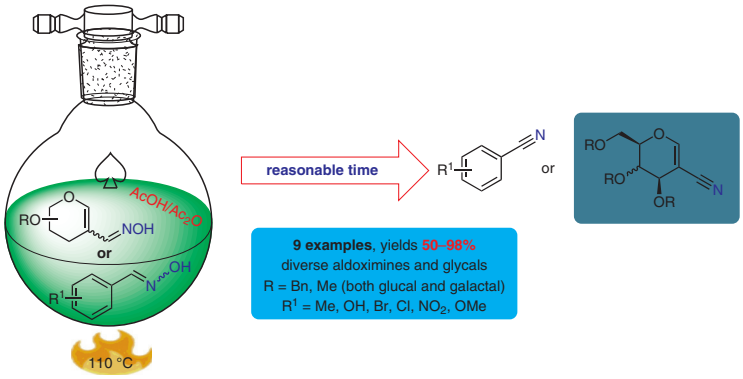

Received: 01.02.2020
Accepted after revision: 04.03.2020
Published online: 27.03.2020
DOI: 10.1055/s-0040-1708007; Art ID: st-2020-u0065-l

Crowd-Reviewed

Abstract Glycals, 1,2-unsatrated carbohydrates, are versatile building blocks for the synthesis of various scaffolds. Despite their potential to serve as suitable precursors in diversity-oriented synthesis, 2-cyanoglycals are less explored in terms of their synthesis and derivatization. Herein, we report a combination of Ac_2O and AcOH as new and efficient dehydrating agent of aldoximes for the synthesis of 2-cyanoglycals. In comparison to the conventional dehydrating system of Ac_2O-base (such as NaOH, NaOAc and K_2CO_3), the current protocol provides superior yields and faster reaction rates. The scope and limitations of the dehydrating system are investigated.

Key words aldoximes, 2-cyanoglycals, nitriles

Nitriles are versatile precursors that can be easily transformed into a variety of functional groups such as amidines, amides, imidoesters, benzamidines, amines, heterocycles, and aldehydes.[1] Besides its ease of derivatization, the nitrile functional group is a key structural unit found in a number of drugs (e.g., Escitalopram, Etravirine, Bicalutamide, Febuxostat, Letrozole, Cyamemazine, Gallopamil, Alogliptin, and Nilvadipine) and biologically active compounds.[1] Moreover, the lone pair of electrons of the nitrogen from a nitrile functional group chelates with metals in the preparation of complexes and also serves as a directing group in C–H activation reactions.[2–10] Owing to its plethora of applications, preparation strategies are continuously being developed. Approaches include the nucleophilic substitution of alkyl halides or aryl diazonium salts (Sandmeyer reaction) with a cyanide,[11] transition-metal-catalyzed cyanation of aryl halides and triflates[1,12] as well as the dehydration of aldoximes. In terms of simplicity and reduced toxicity, the dehydration of aldoximes is the preferred protocol for its synthesis. Accordingly, alternative dehydrating conditions have been developed that include $[RuCl_2(p\text{-cymene})]_2$/MeCN,[13] chlorosulfonic acid,[14] bromodimethylsulfoniumbromide (BDMS)/MeCN,[15] $Pd(OAc)_2/PPh_3$/MeCN,[16] $Zn(acac)_2/H_2O$/toluene,[17] $Cu(OAc)_2$/MeCN,[18] $FeCl_3$/DMF,[19] Fe_3O_4 nanoparticles/DMF,[20] and $TiCl_4$/pyridine.[21] Notably, the use of acetic anhydride as a readily available dehydrating agent in the absence or presence of bases such as NaOH, NaOAc, and K_2CO_3 are also reported as favorable alternatives.[22]

In a continuation of our efforts to develop methodologies for the transformation of glycals into precursors suitable for diversity oriented synthesis (DOS),[23,24] we required access to 2-cyanoglycals **2a** (Table 1) in order to use them as precursors for the synthesis of various scaffolds. The nitrile functional group can be transformed into various 2-C branched sugar derivatives and glycomimetics.[25] Furthermore, with the advance of C–H activation and transition-metal-catalyzed coupling reactions, the ready availability of novel α,β-unsaturated systems such as the 2-cyanoglycals **2a** are crucial to expand the scope and diversity of these reactions. Despite their potential, there is only one low-yielding (<42%) method reported for the synthesis of 2-cyanoglycals that involves the reaction of glycals with chlorosulfonyl isocyanate.[26] In this communication, we describe a new approach to the preparation of 2-cyanoglycals, and their potential in DOS is demonstrated by their transformation into an interrupted-Ferrier product.

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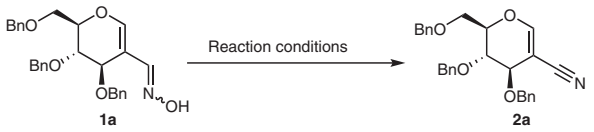
Table 1 Optimization of the Dehydration of Aldoxime **2a**



Entry	Ac_2O (mL)	Additive (1 equiv)	Temp (°C)	Time (h)	Yield (%)[a]
1	1	–	85–145	24	NP
2	1	K_2CO_3	110	16	50
3	1	AcOH	25	24	NP
4	1	AcOH	65	24	NP
5	1	AcOH	85	24	NP
6	1	AcOH	110	8	72
7	–	AcOH	110	8	NP

[a] NP = no product formed.

In our current investigation, we prepared a solution of **1a** in Ac_2O, which was stirred for 8 h at room temperature on the basis of a report that Ac_2O alone can dehydrate aldoximes.[22] When TLC analysis indicated no formation of a new product, the reaction mixture was heated at 85, 110, and 145 °C successively, each for 24 h (Table 1, entry 1). The reaction, however, did not lead to product formation, thereby justifying the need for an additive. As is commonly employed, the use of a base additive (e.g., K_2CO_3)[22d] provided the desired 2-cyano glucal **2a** with a lower yield of 50% after stirring at 110 °C (after trying different temperatures from room temperature) for 16 h under alkaline conditions (entry 2). In the search for a variant that can work under acidic conditions, a combination of AcOH–Ac_2O under various reaction conditions was investigated. After screening of the conditions (entries 3–5), the use of AcOH/Ac_2O (1:1.75, 2 mL) at 110 °C yielded the 2-cyano glucal **2a** with a superior yield of 72% and a shorter reaction time of 8 h (entry 6). Carrying out the reaction in AcOH but in the absence of Ac_2O, no desired product was formed, suggesting the importance of the anhydride in dehydrating the aldoxime group (entry 7). The only difference between K_2CO_3 and acetic acid as additives is the yield and the reaction time as mentioned above; however, both methods can be utilized in nitrile formation. The positive advantage for both will only be shown when base- or acid-sensitive substrates are used for nitrile formation.

The structure of the 2-cyano glucal **2a** was elucidated based on HRMS, NMR and IR spectroscopy. Among others, the disappearance of the signal of the aldoxime proton that appeared at δ_H = 7.67 ppm in the starting material confirmed the successful dehydration of the aldoxime functional group. The C≡N stretch at 2214.3 cm^{-1} in the IR spectrum of the product, further supported a successful dehydration reaction. The identity of the 2-cyano glucal **2a** was further confirmed by single-crystal X-ray diffraction (SCD) analysis (Figure 1) of the methyl protected analogue **2d** (see below).[27] Needle-like crystals of diffraction quality for **2d** were grown by the slow evaporation method. The crystal data collected at 298 K revealed that **2d** crystallizes in the monoclinic space group $P2_1$. In the molecule, there are weak interactions between the neighboring molecules: hydrogen bonding [N···H (2.823 Å), O···H (3.527 Å)] originating from terminal methyl groups, nitrile propagating along the *a*-axis. Also, along *c*-axis, there is C–H···π (3.793 Å) stacking involving two independent glycal rings that links the molecules into a supramolecular structure (see the Supporting Information, Figure S1).

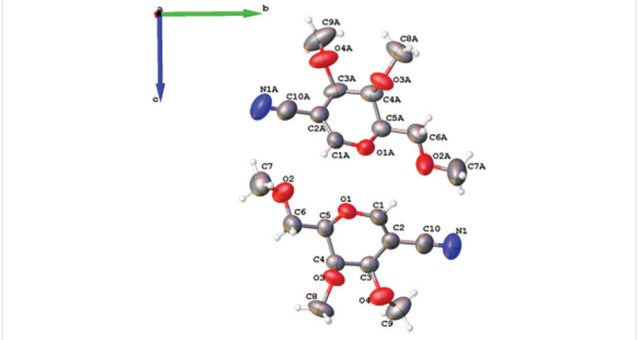
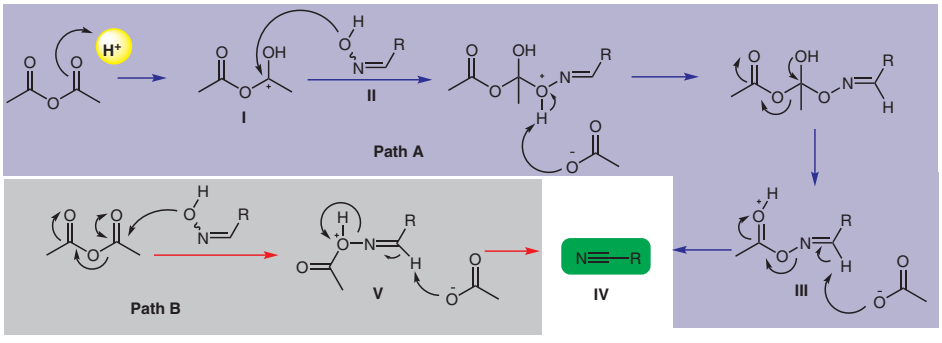


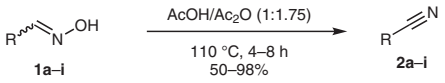
Figure 1 ORTEP molecular structure of **2d** drawn at the 50% probability



Scheme 1 Proposed mechanism of the dehydration reaction

Under the optimal conditions,[28] aldoximes **1b–d** were stirred in a mixture of AcOH/Ac_2O according to Table 2 at 110 °C to give the corresponding 2-cyanoglycals in high to excellent yields and in short reaction time without the formation of the possible Beckman rearrangement product (entries 1–4). Furthermore, the substrate scope of the reaction was examined with various aryl aldoximes possessing either electron-withdrawing or electron-donating groups (entries 5–9). The results are summarized in Table 2; the scope and yields compare favorably with the reported K_2CO_3–Ac_2O protocol for the aldoximes bearing electron-withdrawing groups.[22d] However, lower yields were obtained when aryl aldoximes possessing electron-donating groups were employed as substrates (entry 8).

Table 2 Dehydration of Aldoximes Using the Ac_2O/AcOH Reaction System at 110 °C



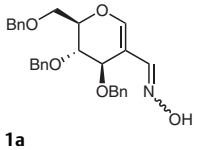
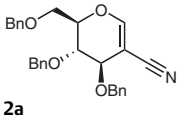
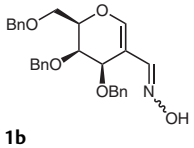
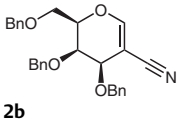
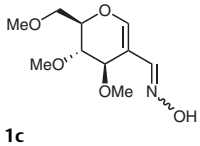
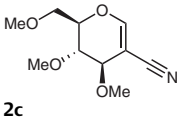
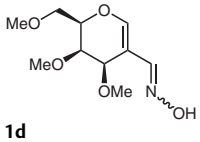
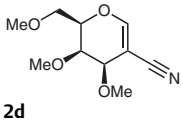
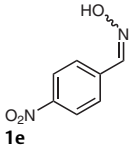
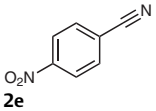
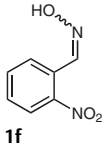
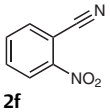
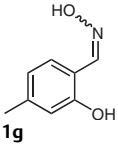
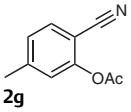
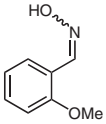
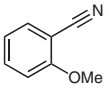
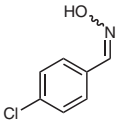
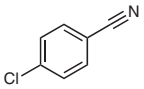
Entry	Substrate	Product	Yield (%)
1	 **1a**	 **2a**	72[a]
2	 **1b**	 **2b**	77[a]
3	 **1c**	 **2c**	74[b]
4	 **1d**	 **2d**	90[b]
5	 **1e**	 **2e**	97[c]
6	 **1f**	 **2f**	92[a]

Table 2 (continued)

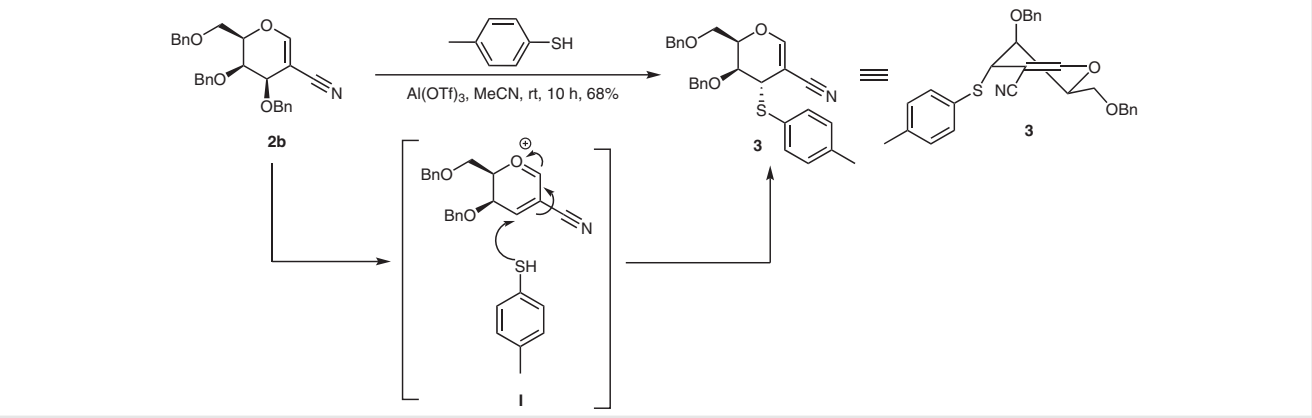
Entry	Substrate	Product	Yield (%)
7	 **1g**	 **2g**	98[c]
8	 **1h**	 **2h**	50[a]
9	 **1i**	 **2i**	70[c]

[a] Reaction run for 8 h.
[b] Reaction run for 6 h.
[c] Reaction run for 4 h.

A proposed mechanism for the dehydration reaction is outlined in Scheme 1. The reaction may commence with the activation of the acetic anhydride by the acetic acid to form complex **I**, considering the acidic conditions of the reaction. This complex then delivers an acyl group to the hydroxyl group of the aldoxime **II** to yield the oxonium intermediate **III** along with equimolar amounts of acetic acid and acetate (Path A). Abstraction of the imine proton in the oxonium intermediate **III** by the acetate promotes deacetylation with the subsequent formation of the nitrile functional group in the final product **IV**.

Alternatively, the hydroxy group might attack the carbonyl group of the acetic anhydride without the involvement of the acetic acid to provide oxonium intermediate **V**, which, upon abstraction of the imine proton, leads to formation of the desired product (Path B). However, it is unlikely that the formation of the nitriles is through Path B since the use of acetic anhydride alone was not favored (Table 1, entry 7).

The strategy provided access to a series of these valuable 2-cyanoglycals **2a–d** and a simple derivatization by treating a solution of 2-cyano galactal **2b** in MeCN with 4-methylthiophenol and catalytic amount of $Al(OTf)_3$ produced the interrupted-Ferrier product, 2-cyano galactal **3** demonstrating their potential use in diversity oriented synthesis as shown in Scheme 2. The absence of the formation of a Ferrier product (2,3-unsaturated galactoside) or a Michael addition product suggests that the cyano group at position C-2 influences the reactivity of glycals in a similar fashion to formyl groups.[29] The molecular structure of **3** was further confirmed by SCD analysis (Figure 2). The structure crystallizes in the monoclinic space group $P2_1$.



Scheme 2 Interrupted-Ferrier rearrangement of 2-cyano galactal **2b**

The half-chair conformation of the galactal ring propagates along <001> plane. The crystal packing of the molecule is dominated by hydrogen bonding in a similar fashion to that in structure **2d**. The disordered phenyl ring was modeled to refine the occupancy ratio of 0.55:0.45 with about two position atoms: C8-C15 and C8A-C15A. All non-hydrogen atoms were refined anisotropically (see the Supporting Information, Figure S2).

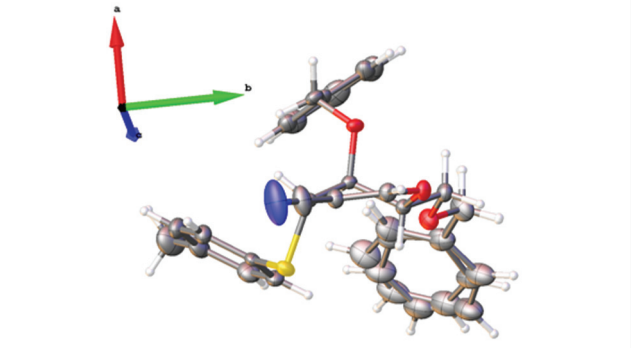


Figure 2 ORTEP molecular structure of **3** drawn at the 50% probability

In conclusion, we have demonstrated that a combination of AcOH and Ac_2O can be employed as a new dehydrating system for the preparation of nitriles from the corresponding aldoximes. Furthermore, the strategy was used in the synthesis of 2-cyanoglycals, which are potential precursors for the transformation of glycals in diversity oriented synthesis. To our knowledge, this is the first report in which a combination of Ac_2O with an acid (in this case AcOH) is used to facilitate dehydration of aldoximes. The short reaction time, high chemoselectivity, and high yields make the method an attractive alternative in organic synthesis.

Funding Information

We acknowledge the South African Agency for Science and Technology Advancement (NRF 118552) for funding.

Acknowledgment

We thank the Centre for Synthesis and Catalysis of the University of Johannesburg (UJ). We are indebted to the UJ-Spectrum NMR facility at University of Johannesburg.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1708007.

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(28) **Typical procedure:** A solution of pre-prepared aldoxime **1a** (100 mg, 0.218 mmol) in $AcOH/Ac_2O$ (1:1.75, 2 mL) in a 10 mL round-bottom flask fitted with a condenser was heated at 110 °C for 4 h under a nitrogen atmosphere. The reaction mixture was then allowed to cool to room temperature and 15% aq. NaOH was added until the solution became slightly basic. The resultant mixture was extracted with ethyl acetate and the combined organic phases were washed successively with saturated bicarbonate, brine and water, dried over $MgSO_4$ and concentrated to dryness. The residue product was purified by column chromatography on silica gel using a mixture of ethyl acetate/hexane (9:1) as eluent to provide 2-cyanoglucal **2a** in 72% yield.

Compound 2a: Yield: 72%; colorless oil. IR (neat): 2214.3 cm^{-1} (C≡N). HRMS: *m*/*z* [M + Na]$^+$ calcd: 441.1940; found: 441.1835. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.40–7.23 (m, 15 H, Ar), 7.15 (s, 1 H, H1), 4.78 (d, *J* = 11.5 Hz, 1 H, -CH_{1a}Ph), 4.70–4.55 (m, 3 H, -CH_2Ph and -CH_{1b}Ph), 4.50 (s, 2 H, -CH_2Ph), 4.39 (q, *J* = 14.8 Hz, 1 H, H5), 4.14 (d, *J* = 4.8 Hz, 1 H, H3), 3.86 (t, *J* = 10.4 Hz, 1 H, H4), 3.77 (dd, *J* = 6.0, 11.0 Hz, 1 H, H6_a), 3.68 (dd, *J* = 3.5, 14.5 Hz, 1 H, H6_b). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.0 (C1), 137.5, 137.2, 137.1, 128.6, 128.5, 128.4, 128.2, 128.1, 128.06, 128.0, 127.9, 127.8, 127.7 (Ar), 117.9 (C2), 89.1 (CCN), 77.9 (C5), 73.5, 73.1, 72.6 (CH_2Ph×3), 71.9 (C3 and C4), 67.5 (C6).

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