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4-Isopropyl-2-oxazolin-5-one Anion as a New Convenient Formyl Anion Equivalent for Conjugate Addition and Aldol Reactions.

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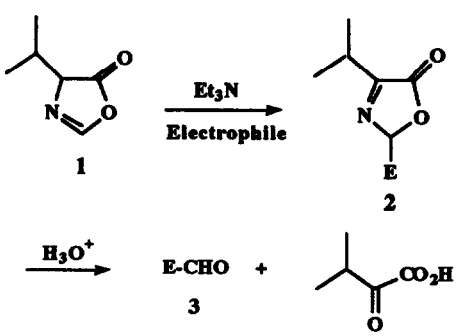
Abstract: The anion of the title compound, simply generated in the presence of catalytic amount of triethylamine, acts as nucleophilic acylating equivalent of formaldehyde reacting with both common electrophilic olefins or aldehydes to give moderate to good yield of Michael or aldol adducts respectively, which are easily hydrolyzed by dilute acid at ambient temperature to afford the corresponding aldehydes.

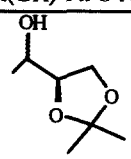
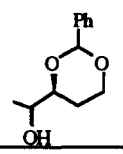
Methods for reversing temporarily the characteristic reactivity, nucleophilic or electrophilic, of an atom or group have continued to hold a fascination for the synthetic organic chemist for many decades.[1] Certainly, there is no paucity in the variety or quantity of approaches by which the normally electrophilic carbon of a carbonyl group can be transformed into a nucleophilic carbon. Indeed, this area of organic synthesis has been consistently well-documented by ample review articles[2] and references concerning the interesting and novel chemistry appeared in the last years can be found in two recent papers by Katritzky et al.[3,4], dealing with the development of new acyl- and formyl anion equivalents.[5]

We wish to report in this communication the use of the anion of **1**[6], simply generated in the presence of a catalytic amount of triethylamine, as a new convenient masked synthon of formyl anion.



Surprisingly, in spite of the vast amount of accumulated informations about the rich and varied chemistry of 5(4)-oxazolones,[7] including the use of 2-substituted-5(4H)-oxazolones as acyl anion equivalent,[8] to the best of our knowledge, the synthetic potential of 4-isopropyl-2-oxazolin-5-one **1** as synthetic equivalent of the formyl anion has remained hitherto unexplored, although it has been widely utilized as starting material for the preparation of heterocyclic compounds or as activating agent for the carboxylic group.[7]

Reaction of **1** with selected electrophiles such as α,β-unsaturated compounds or aldehydes proceeded smoothly between 0°C and room temperature producing the well-characterized adducts **2*** in moderate to excellent yield, through exclusive carbon-carbon bond formation at the carbon attached to two heteroatoms. The isolated adducts were subsequently hydrolyzed at room temperature by treatment with dilute acid, the released aldehydic compounds **3** being easily separated from the α-ketoacid derived by cleavage of the heterocyclic system by washing with aqueous $NaHCO_3$.** Our preliminary results are summarized in the following Table:

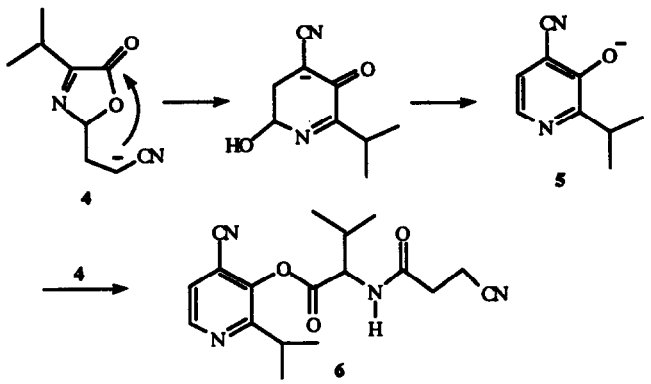
Entry	Electrophile	E	2 % yield	3 % yield
a	CH_2=CH-CHO	-CH_2-CH_2-CHO	72	38
b	CH_2=CH-CO-CH_3	-CH_2-CH_2-CO-CH_3	70	76
c	CH_2=CH-CO_2Me	-CH_2-CH_2-CO_2Me	68	72
d	CH_2=CH-CO-(CH_2)7-CO_2Me	-CH_2-CH_2-CO-(CH_2)7-CO_2Me	55	80
e	2-Cyclohexen-1-one	3-Cyclohexanone	45	84
f	2-cyclopenten-1-one	3-Cyclopentanone	52	70
g	CH_2=CH-NO_2 [a]	-CH_2-CH_2-NO_2	90	64
h	CH_3CHO	-CH(OH)CH_3	61	44[b]
i	PhCHO	-CH(OH)Ph	89	51[b]
j	o-NO_2-PhCHO	-CH(OH)-Ph-o-NO_2	93	37[b]
l	2,3-*O*-isopropylidene-2R,3-dihydroxypropanal		78[c]	59[d]
m	2,4-*O*-benzylidene-2S,4-dihydroxybutanal		66[c]	49[e]

[a] Generated *in situ* from the corresponding β-hydroxybenzoate. [b] Isolated as dimeric compounds. [c] The yield is referred to the mixture of diastereomers. [d] Isolated as (D)-erhytrose. [e] Isolated as peracylated (L)-4-deoxyribose, m.p. 86-87°C, $[\alpha]^{D}_{25}$= +51°(c 1.3, $CHCl_3$).

Interestingly, the addition in a conjugate fashion of the anion of **1** to linear enones followed by acid hydrolysis of the resulting addition products furnished γ-dicarbonyl compounds, which are known precursors of 2-substituted-2-cyclopenten-1-ones. Thus, methyl 5-oxocyclopentene-1-heptanoate, a widely utilized

intermediate for prostaglandin synthesis, could be conveniently obtained by cyclization under reported conditions[9] of methyl 9,12-dioxododecanoate (entry **d**).

The reaction of **1** with acrylonitrile offered a notable exception to the trend of reactivity shown by the investigated α,β-unsaturated compounds, producing unexpectedly the crystalline 2,3,4-trisubstituted pyridine derivative **6** (m.p.139-141°C), the structure of which has been confirmed by X-ray crystallographic analysis.



Its formation can be explained through an intramolecular attack of the α-carbon of the nitrile of the initially adduct **4** to the carbonyl group of the oxazolinone ring system leading with concomitant dehydration to the intermediate 2-isopropyl-3-hydroxy-4-cyanopyridine **5**, subsequently undergoing intermolecular O-acylation by **4** to give **6**

Nucleophilic addition of the anion of **1** to different simple aldehydes (entries **h-j**) proceeded uneventfully affording the expected 1,2-adducts. Unfortunately, the regeneration of the aldehydic function from these adducts resulted in the formation of dimers, despite the mild conditions involved.[10]

The readily available D(+)-glyceraldehyde acetonide (entry **l**) and 2,4-O-benzylidene-2,4-dihydroxybutanal (entry **m**), obtained starting from L-malic acid, reacted as the counterpart of **1**, forming a mixture of diastereoisomers. Interestingly, in both cases, the most abundant stereoisomer (7:3) could be easily separated by flash chromatography, the first as a white solid, m.p. 90-91°C, $[\alpha]^{D}_{25} = -75°$ (c 0.8, MeOH), the other one as colorless oil, $[\alpha]^{D}_{25} = +13.6°$ (c, 0.8 MeOH).

Acid-promoted regeneration of the aldehydic function proceeded with concomitant hydrolysis of the diol protective groups producing respectively D(-)-erhytrose and (L)-4-deoxyribose, the structure of the latter being inferred after peracetylation, allowing to establish the configuration of the newly created stereocenter of the homologated chain.

In conclusion, the extremely mild conditions required for proton abstraction, the good reactivity of the anion and the mild single-step hydrolytic conditions makes the anion of **1** a very attractive nucleophilic acylating equivalent of formaldehyde, especially as a tool for obtaining 1,4-dicarbonyls and as homologating agent in sugar chemistry.

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References and Notes.

1. Ager, D.J. in "*Unpoled Synthons: A Survey of Sources and Uses in Synthesis*"; Hase, T.A., Ed.; John Wiley and Sons, Inc.:New York, 1987; pp. 19-72.
2. Leber, O.W. Tetrahedron, **1976**, 32, 1943-1971.
3. Katritzky, A.R.; Yang, Z.; Lam, J.N. J. Org. Chem. **1991**, 56, 2143-2147.
4. Katritzky, A.R.; Yang, Z.; Lam, J.N. J. Org. Chem. **1991**, 56, 6917-6923.
5. A new formyl anion equivalent has been recently proposed: Lassaletta, J-M.; Fernandez, R. Tetrahedron Lett. **1992**, 33, 3691-3694.
6. Siemion, I.Z.; Nowak, K. Roczniki Chemii **1961**, 35, 979-984. Compound **1** can be easily prepared by DCC-promoted dehydration of N-formylvaline followed by Kugelrohr distillation (0.05 mmHg) without aqueous work-up. This compound is sensitive to moisture and hydrolyze rapidly in the atmosphere, but can be stored under nitrogen at ambient temperature.
7. Boyd, G. V. in "*Comprehensive Heterocyclic Chemistry*", Pott, K. T. Ed., Pergamon Press, 1984; pp. 177-233.
8. Lohmar, R.; Steglich, W., Angew. Chem. Int. Ed. Engl., **1978**, 17, 450-
9. Reuter, J.M.; Salomon, R.G. J. Org. Chem. **1978**, 43, 4247-4248.
10. Oldenziel, O.H.; van Leusen, A. M. Tetrahedron Lett. **1974**, 15, 167-170 and references quoted therein.

*. All new compounds gave satisfactory analytical and spectroscopic data. Selected ^{1}H NMR ($CDCl_3$): **2a**: δ 1.29 (d, 6H, J=6.88Hz), 2.0-2.4 (m, 2H), 2.7 (t, 2H, J=7Hz), 3.0 (m, 1H), 9.8 (s, 1H); **2c**: δ 1.28 (d, 6H, J=7Hz), 2.0-2.4 (m, 2H), 2.5 (t, 2H, J=7.24Hz), 3.0 (m, 1H), 3.7 (s, 3H), 5.95 (m, 1H); **2d**: δ 1.1-1.4 (m, 6H), 1.28 (d, 6H, J=7Hz), 1.45-1.70 (m, 4H), 1.9-2.1 (m, 1H), 2.1-2.25 (m, 1H), 2.3 (t, 2H, J=7.5Hz), 2.43 (t, 2H, J=7.5Hz), 2.56 (t, 2H, J=7.5Hz), 2.85-3.1 (m, 1H), 3.66 (s, 3H), 5.90 (m, 1H); **2l**: δ 1.29 (d, 6H, J=7Hz), 1.38 (s, 3H), 1.47 (s, 3H), 2.99 (m, 1H), 3.22 (bs, 1H), 3.99-4.16 (m, 3H), 4.25-4.3 (m, 1H), 6.15 (m, 1H); **3d**: δ 1.30 (m, 6H), 1.58 (m, 4H), 2.3 (t, 2H, J=7.3Hz), 2.46 (t, 2H, J=7.3Hz), 2.75 (m, 4H), 3.66 (s, 3H), 9.80 (s, 1H); **3f**: δ 2.4 (m, 4H), 2.36 (dd, 1H, J=18.6Hz, J=7.4Hz), 2.5 (dd, 1H, J=18.6Hz, J=7.4Hz), 3.24 (m, 1H), 9.77 (d, 1H, J= 1.47Hz); **6**: δ 1.13 (t, 6H, J=7Hz), 1.23 (d, 3H, J=6.7Hz), 1.25 (d, 3H, J=6.7Hz), 2.4-2.6 (m, 1H), 2.71 (m, 4H), 3.1-3.4 (m, 1H), 4.92 (dd, 1H, J=8.76Hz, J=4.88Hz), 6.3 (d, 1H, J=10Hz), 7.41 (d, 1H, J=4.8Hz), 8.65 (d, 1H, J=4.8Hz).

. General procedure: To a solution of **1 (0.01mmol) in CH_2Cl_2 (10ml) containing a few drops of triethylamine Michael acceptor (0.01mmol) or aldehyde (0.01mmol) is added at 0°C and the mixture left at room temperature until completion (TLC control). The solvent was evaporated at reduced pressure and the residue was purified by flash chromatography (ether : petroleum ether 1:1) to afford **2**.

A solution of **2** (0.01mol) in THF (10ml) was stirred at room temperature overnight with 5% hydrochloric acid (5ml). The solvent was evaporated under reduced pressure, the residue was taken with water (10ml), extracted with EtOAc (3x15ml), the extracts washed with aqueous $NaHCO_3$, dried and evaporated to leave **3**. Washing with $NaHCO_3$ was omitted in the case of water-soluble compounds (entries **l-m**), which were isolated, after extraction by AcOEt of the formed α-ketoacid, by concentration in vacuo of the aqueous solution to dryness.

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