Synthesis and transformations of picrylacetaldehyde

Vasilii M. Vinogradov, Igor L. Dalinger, Aleksei M. Starosotnikov and Svyatoslav A. Shevelev*

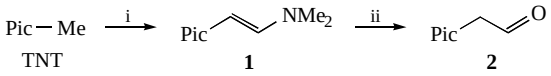
N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 117913 Moscow, Russian Federation.
Fax: +7 095 135 5328; e-mail: shevelev@cacr.ioc.ac.ru

10.1070/MC2000v010n04ABEH001322

A method for the synthesis of picrylacetaldehyde was developed, and its reactivity was examined.

In the context of chemical utilisation of 2,4,6-trinitrotoluene (TNT),[1] we developed a procedure for preparing picrylacetaldehyde starting from TNT. This previously unknown aldehyde is of interest as a new building block because of the presence of a highly reactive formyl group, an active methylene unit, nitro groups, and an aromatic ring of the picryl moiety (nucleophilic substitution for nitro groups, vicarious and oxidative nucleophilic substitution for hydrogen, *etc.*).

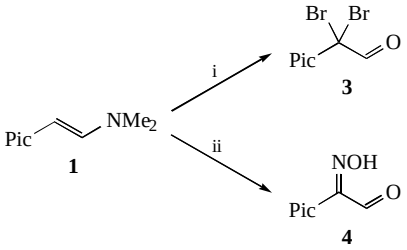
Picrylacetaldehyde **2** was prepared by acidic hydrolysis of β-dimethylamino-2,4,6-trinitrostyrene **1**, which in turn was readily formed by TNT condensation with dimethylformamide dimethyl acetal.



TNT **1** **2**

Reagents and conditions: i, 1 equiv. $H_2NCH(OMe)_2$, toluene, 20 °C, 24 h, 70% yield; ii, 2 M HCl in $H_2O/CHCl_3$, 61 °C, 5 h, 78% yield.

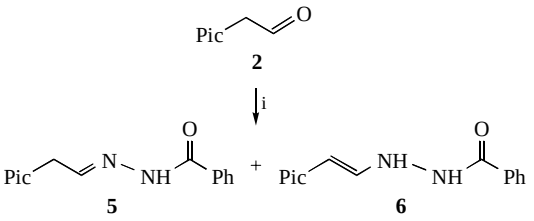
Enamine **1** can be used as a masked form of picrylacetaldehyde because it easily undergoes hydrolysis in acidic media. For example, bromination and nitrosation of **1** results in picrylacetaldehyde modified at the methylene group



Reagents and conditions: i, 1 equiv. Br_2, $CHCl_3$, 20 °C, 5 h, 52% yield; ii, 2 equiv. $NaNO_2$, HCl (conc.), 20 °C, 3 h, 66% yield.

The same products (**3** and **4**) were also obtained using picrylacetaldehyde as the starting compound.

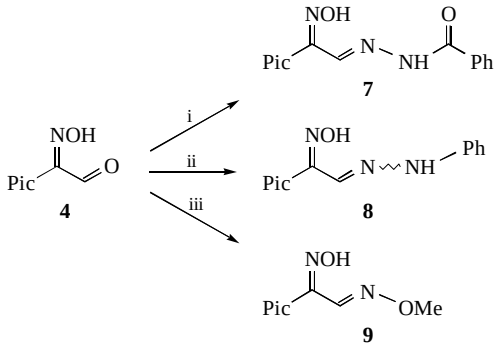
A tendency to deformylation under the action of even weak bases such as pyridine with the regeneration of TNT is a characteristic property of picrylacetaldehyde. In particular, for this reason picrylacetaldehyde does not form arylhydrazones and oximes with arylhydrazines and hydroxylamine. Hydrazone **5** was formed only by the interaction of picrylacetaldehyde with an extremely weak base, benzoic acid hydrazide. We also detected a trace impurity of tautomer **6**.



Reagents and conditions: i, 1 equiv. $PhCONHNH_2$, EtOH, 78 °C, 1 h, 80% yield of **5**.

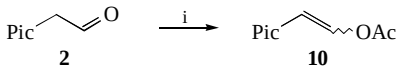
At the same time, under neutral and acidic conditions, picrylacetaldehyde behaves as a typical aliphatic aldehyde. Picrylglyoxal monooxime **4**, which is a picrylacetaldehyde derivative without an α-methylene group, exhibit similar properties.

Oxime **4** gives with nitrogen nucleophiles usual derivatives at the formyl group. Apart from benzoic acid hydrazide, phenylhydrazine and *O*-methylhydroxylamine also react with oxime **4**.



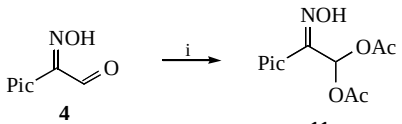
Reagents and conditions: i, 1 equiv. $PhCONHNH_2$, EtOH, 78 °C, 3 h, 61% yield; ii, 1 equiv. $PhNHNH_2 \cdot HCl$, EtOH, 78 °C, 3 h, 91% yield; iii, 1 equiv. $MeONH_2$, EtOH, 78 °C, 3 h, 76% yield.

The acylation of picrylacetaldehyde with acetic anhydride afforded enol acetate **10**



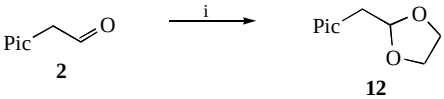
Reagents and conditions: i, Ac_2O, 80–90 °C, 78% yield, $E/Z \approx 1:2$.

The acylation of picrylacetaldehyde derivative **4** having no methylene group resulted in acylal **11**.



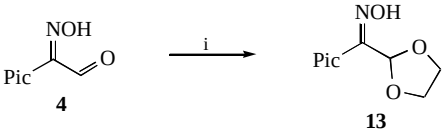
Reagents and conditions: i, Ac_2O, 80–90 °C, 5 h, 89% yield.

Picrylacetaldehyde with ethylene glycol forms cyclic acetal **12**.



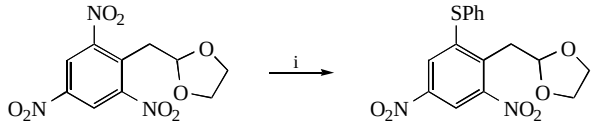
Reagents and conditions: i, 2 equiv. $HO(CH_2)_2OH$, 0.1 equiv. TsOH, benzene, 81 °C, 2 h, 95% yield.

Oxime **4** also forms analogous acetal **13** under more severe conditions.



Reagents and conditions: i, 2 equiv. $HO(CH_2)_2OH$, 0.1 equiv. TsOH, toluene, 110 °C, 5 h, 87% yield.

As a protected aldehyde, dioxolane **12** is stable to alkaline media. Using the reaction with thiophenol in *N*-methylpyrrolidone in the presence of K_2CO_3 as an example, we found the nucleophilic substitution for a nitro group in **12**.

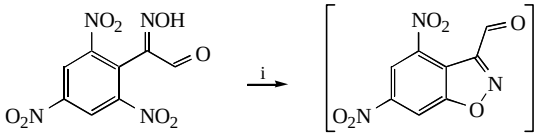


12 **14**

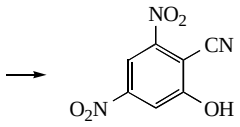
Reagents and conditions: i, 1 equiv. PhSH, 1 equiv. K_2CO_3, *N*-methylpyrrolidone, 20 °C, 24 h, 32% yield.

The reaction is regioselective: only the *ortho*-nitro group was replaced, and sulfide **14** was formed.

In contrast to picrylacetaldehyde, under the action of bases, oxime **4** forms 2-cyano-3,5-dinitrophenol **16**. 3-Carbonyl-4,6-dinitro-1,2-benzisoxasole **15** is a probable intermediate.



4 **15**



16

Reagents and conditions: i, 1 equiv. K_2CO_3, EtOH, 20 °C, 24 h, 75% yield.

Such benzisoxasoles are unstable in alkaline media and are transformed into salicylic acid nitriles.[2]

All of the compounds prepared were characterised by physicochemical methods.†

† ^{1}H NMR spectra were measured on a Bruker AM 300 spectrometer in [$^2H_6$]DMSO with TMS as a standard.

1: mp 155–157 °C (toluene) (lit.,[3] 155–157 °C).

2: mp 90–91 °C ($CHCl_3$). ^{1}H NMR, δ: 4.5 (s, 2H, CH_2), 9.0 (s, 2H, H_{arom}), 9.8 (s, 1H, O=CH).

3: mp 149–151 °C ($CHCl_3$). ^{1}H NMR, δ: 8.9 (s, 2H, H_{arom}), 9.2 (s, 1H, O=CH).

4: mp 108–110 °C ($CHCl_3$). ^{1}H NMR, δ: 9.1 (br. s, 1H, OH), 9.2 (s, 2H, H_{arom}), 9.8 (s, 1H, O=CH).

5: mp 198–200 °C (decomp.) (EtOH). ^{1}H NMR, δ: 4.1 (s, 2H, CH_2), 7.2–7.6 (m, 4H, Ph, HC=N), 7.8 (m, 2H, Ph), 9.0 (2H, Pic), 11.4 (1H, NH).

7: mp 142–145 °C (EtOH). ^{1}H NMR, δ: 7.4–7.6 (m, 3H, Ph), 7.7–7.9 (m, 2H, Ph), 8.5 (s, 1H, N=CH), 9.1 (s, 2H, Pic), 11.9 (s, 1H, NH), 12.7 (s, 1H, OH).

8: mp 126–127 °C ($CHCl_3$). ^{1}H NMR (major stereoisomer) δ: 6.7–6.8 (m, 3H, Ph), 7.0–7.2 (m, 2H, Ph), 7.8 (s, 1H, N=CH), 9.1 (s, 2H, Pic), 10.6 (s, 1H, NH), 12.0 (s, 1H, OH).

This work was supported by the International Science and Technology Center (ISTC), project no. 419.

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Received: 16th May 2000; Com. 00/1648

9: mp 154–156 °C ($CHCl_3$). ^{1}H NMR, δ: 3.8 (s, 3H, OMe), 8.0 (s, 1H, N=CH), 9.1 (s, 2H, H_{arom}), 12.8 (s, 1H, OH).

10: mp 71–75 °C (*E*/*Z* mixture). ^{1}H NMR δ: (*Z*)-isomer, 2.0 (s, 3H, Me), 6.3 (d, 1H, α-H, ^3J 6.9 Hz), 7.5 (d, 1H, β-H, ^3J 6.9 Hz), 9.0 (s, 2H, Pic); (*E*)-isomer, 2.0 (s, 3H, Me), 6.7 (d, 1H, α-H, ^3J 12.7 Hz), 7.4 (d, 1H, β-H, ^3J 12.7 Hz), 9.1 (s, 2H, Pic).

11: mp 178–180 °C (EtOH). ^{1}H NMR, δ: 2.0 (s, 6H, 2Me), 2.05 (s, 3H, Me), 7.7 [s, 1H, $CH(OAc)_2$], 9.3 (s, 2H, Pic).

12: mp 102–104 °C (EtOH). ^{1}H NMR, δ: 3.6 (d, 2H, CH_2, ^3J 4.2 Hz), 3.6–3.8 [dm, 4H, $O(CH_2)_2O$], 5.15 (t, 1H, OCHO, ^3J 4.2 Hz), 8.95 (s, 2H, Pic).

13: mp 85–87 °C (EtOH). ^{1}H NMR, δ: 3.6–3.9 [dm, 4H, $O(CH_2)_2O$], 5.6 (s, 1H, OCHO), 9.1 (s, 2H, Pic), 12.2 (s, 1H, OH).

14: mp 103–106 °C (EtOH). ^{1}H NMR, δ: 3.6 (d, 2H, CH_2, ^3J 5.3 Hz), 3.7 [m, 4H, $O(CH_2)_2O$], 5.2 (t, 1H, OCHO, ^3J 5.3 Hz), 7.5–7.6 (m, 5H, Ph), 7.9 (s, 1H, arom.), 8.5 (s, 1H, arom.).

16: mp 187–188 °C ($CHCl_3$). ^{1}H NMR, δ: 8.0 (d, 1H, arom., ^4J 2.0 Hz), 8.3 (d, 1H, arom., ^4J 2.0 Hz); this compound was described in ref. 4; however, the melting point was not given.