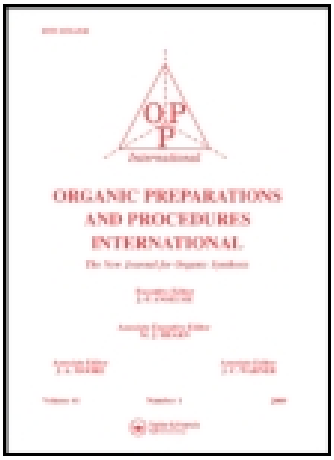

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A Simplified Method for the Efficient Preparation of Pivaloylacetonitrile

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OPPI BRIEF

A Simplified Method for the Efficient Preparation of Pivaloylacetonitrile

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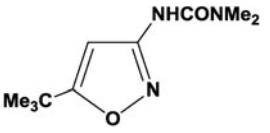
Pivaloylacetonitrile (**2**, cyanopinacolone or 4,4-dimethyl-3-oxopentanenitrile) is a crucial intermediate for the synthesis of the isoxazole skeleton of the selective herbicide *isouron* and for the construction of inhibitors of *p38 MAP* kinase based on pyrazolyl ureas.[1]



isouron

There are three methods for the preparation of pivaloylacetonitrile. The first is based on the reaction of methyl or ethyl pivaloate with the anion of acetonitrile[2–7] generated through an electrochemical process[2] or under strongly basic conditions with bases such as alkali metal hydride or alkoxide.[3–6] The process is carried out at very low temperatures in inert solvents such as bromobenzene or THF, for example. An alternate process involves the nucleophilic substitution of halogen of 1-chloro- or 1-bromopinacolone by alkali metal cyanide in protic solvents.[8–10] The third route involves the reaction of ethyl cyanoacetate with *tert*-butyllithium at –70°C in pentane.[11] However, these three methods are not readily applicable on an industrial scale as they involve difficult reaction conditions (very low temperatures), poor selectivity, low conversion of the starting materials, long reaction times and relatively moderate yields (60–78%). Furthermore, some of the starting materials are expensive and/or dangerous to use. We now report a modification of the nucleophilic substitution

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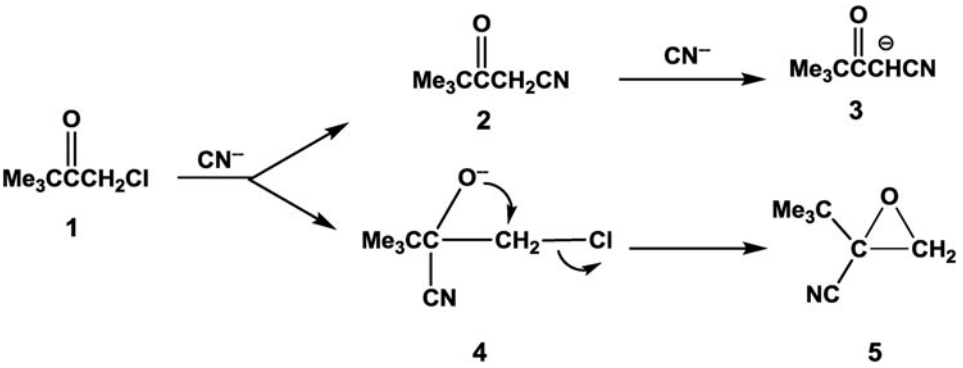
conditions of 1-chloropinacolone with sodium cyanide that removes all disadvantages of these methods. The reaction proceeds more rapidly in increased yields, diminished formation of by-products and waste and with limited use of expensive and dangerous solvents. The effect of the cyanide anion acting as a base or nucleophile on the course of the reaction is illustrated in *Scheme 1*.

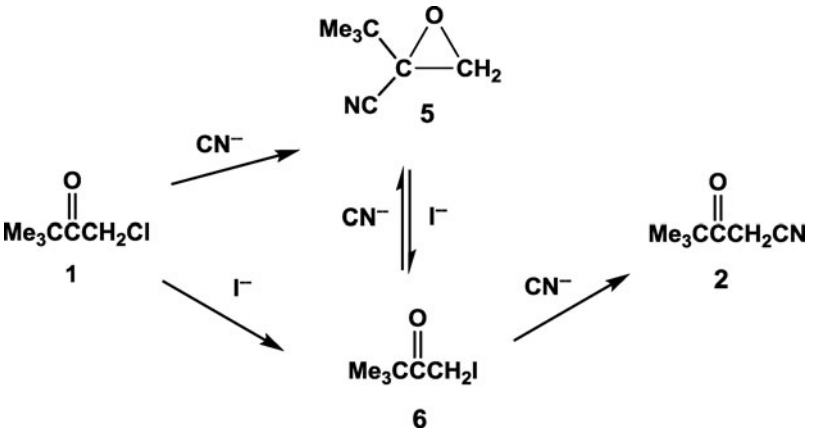


Scheme 1

The main problem of the published routes is the purity of final product because of low-reaction regioselectivity. As described in the literature,[8–12] the target product, pivaloylacetonitrile **(2)**, is contaminated by up to 20–35% of the oxirane **5** and polymeric by-products (*Scheme 1).* The formation of **5** may be explained by nucleophilic addition of cyanide ion to the carbonyl group of 1-chloropinacolone followed by an intramolecular nucleophilic substitution of the chlorine atom to provide the oxirane **5**. The generation of polymer by-products may be the result of intermolecular nucleophilic displacement of the chlorine of the starting material initiated by the carbon atom of the deprotonated (by cyanide ion) cyanomethylene group **3** (or the starting material itself) or by the oxygen atom in an intermediary alcoholate **4**. Carbanion **3** may be generated by removal of a proton by cyanide ion acting as a base on cyanomethylene group of **2** or of the starting material to generate carbanions that undergo further undesirable addition and substitution reactions.

Our simple solution to these difficulties is based on the addition of catalytic amounts of iodide ion (*Finkelstein reaction*)[13] to a reaction mixture containing 1-chloropinacolone (**1**), sodium cyanide and methanol as a solvent. The changes in the reaction pathway resulting from the addition of iodide ion are shown in *Scheme* 2. The iodo intermediate **6** generated *in situ* is not only more reactive than **1** toward the nucleophilic substitution reaction with cyanide ion but its methylene hydrogens are less acidic than those of **1**. Most importantly, nucleophilic attack of the iodide ion of the putative oxirane (**5**) would in effect regenerate the iodo intermediate **6**.

Thus, the Finkelstein procedure using only catalytic amount of iodide ion, is an excellent method for a very simple yet an effective process on an industrial scale.[14,15] The advantages of method are its simplicity, the high conversion of substrate **1** through a highly selective synthesis, mild reaction conditions [temperature 60°C, shorter reaction time (3 h instead of usual 6 h)] and use of a recyclable solvent. Product **2** is easily isolated by



Scheme 2

acidification of the reaction mixture with dilute hydrochloric acid to afford pure **2**. The only waste is the sodium chloride solution in the filtrate after collection of the product.

Experimental Section

The ^{1}H NMR spectrum was recorded in $CDCl_3$ on a Bruker Avance 300 MHz NMR spectrometer. Chemical shifts are reported in δ values, using TMS an internal standard. Melting points were determined on a Boetius microscope with digital thermometer and are uncorrected. GC-MS was acquired on a HP 6890 plus/MS 5973N apparatus (Agilent Technologies). Comparison of all date obtained with those reported in the literature confirmed the identity of the product. 1-Chloropinacolone and sodium cyanide were obtained from Fluka and Lucebni zavody Draslovka a.s. Kolin (Czech Republic), respectively.

4,4-Dimethyl-3-oxopentanenitrile (Pivaloylacetonitrile, 2)

To a stirred and cooled (below 30°C) suspension of finely powdered sodium cyanide (50.5 g, 1.01 mol, 98% purity), sodium carbonate (10.6 g, 0.10 mol) and sodium iodide (3.0 g, 0.02 mol) in methanol (450 ml) in a 1000 ml round bottom flask fitted with a condenser and a magnetic stir bar, was added dropwise (30 minutes) 1-chloropinacolone (134.6 g, 1.0 mol). After 15 min stirring, the reaction mixture was heated to 60°C and stirred for 3 h. The inorganic salts, which precipitated after cooling, were filtered off using suction, washed with 50 ml of methanol and the pH value of filtrate was adjusted to neutral by addition of dil. hydrochloric acid (vol. 1:1). The additional amount of precipitated salts were filtered off using suction again and washed with 50 ml of methanol. The combined methanol solution (300 ml) was evaporated in vacuum and 300 ml of hot water (80–85°C) was added to the oily distillation residue. This heterogeneous two-phase mixture was cooled below 20°C and mixed intensively. The pure solid product formed directly was collected as a colorless crystallic mass to yield 118.9 g (95%) of 99% pure (GC) **2**, mp. 68–69°,

lit.[12] 70°, after a drying in vacuum. ^{1}H NMR: δ 1.24 (s, 9H, 3 × CH_3), 3.50 (s, 2H, CH_2). GC-MS, m/z, M^+ Calcd for $C_7H_{11}NO$: 125.168. Found 126.166.

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