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Hunig's Base-Magnesium Chloride Mediated Carbon Alkylation and Oxygen Acylation of Benzoylacetonitrile

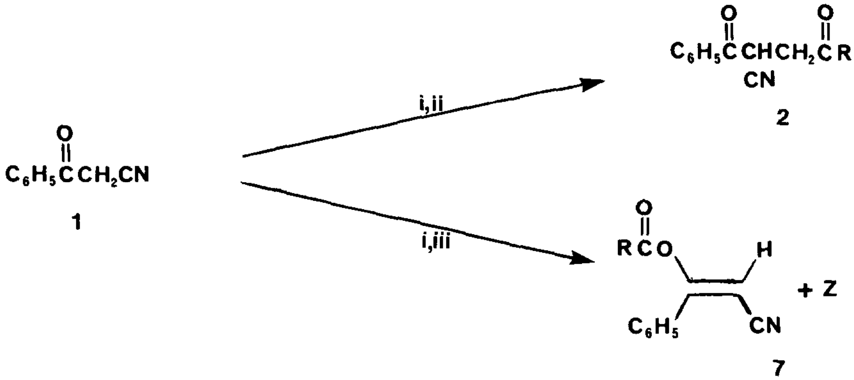
Tarek S. Mansour

Université du Québec, Institut Armand-Frappier, Biochemical Product Division, 531 boulevard des Prairies, Laval, Québec, Canada H7V 1B7

Summary: In the presence of Hunig's base and anhydrous magnesium chloride, benzoylacetonitrile (1) reacts with 2-haloketones and -esters to give C-alkylated products which may cyclize to polysubstituted furans whereas with acid chlorides O-acylated products are obtained as separable mixtures of E and Z isomers.

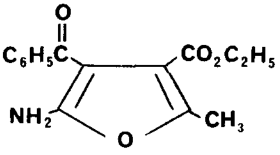
Benzoylacetonitriles are important intermediates for the syntheses of a wide variety of heterocycles[1]. In addition, they undergo facile base-promoted condensation with carbonyl compounds to give Knoevenagel products[2]. The preparation of substituted benzoylacetonitriles has been carried out by acylating nitrile - containing organozinc reagents with symmetrical anhydrides[3] or by acylating stabilized α-lithionitriles with mixed anhydrides[4]. Other procedures include acid hydrolysis of tetraalkoxydihydropyrans[5], substitution reactions of 2-haloketones with tetraalkylammonium cyanide[6] and the Eschenmoser sulfur contraction method of thioamides[7]. Direct cyanation of ketones with chlorosulfonylisocyanate[8] or benzothiocyanate[9] has also been reported. In light of recent reports describing acidity enhancement of carbon acids due to metal salts complexation[10], we have investigated the reaction of benzoylacetonitrile (1) with 2-haloketones and -esters as well as acid chlorides.

When diisopropylethylamine (Hunig's base, DIEA, 2 equiv.) is added to a dichloromethane solution containing anhydrous magnesium chloride (1 equiv.) and (1) at 0°C for 1 hr. followed by slow addition of α-bromoacetophenone (0°C→RT, 4 h.) and acidic workup, 1,4-dicarbonyl compound (2a) is isolated in good yield as shown in Scheme 1. Dialkylated products are not detected. Ethyl iodoacetate, α-bromo-p-methoxyacetophenone and ethyl 4-chloroacetoacetate reacted in a similar fashion.



Scheme 1. i, DIEA, $MgCl_2$, CH_2Cl_2 ii, $RCOCH_2X$ iii, RCOX

In the presence of an additional electron withdrawing group as in ethyl 2-chloroacetoacetate, the corresponding 1,4-dicarbonyl compound was not isolated as it underwent intramolecular enol attack on the cyano group giving 2-amino-3-benzoyl-4-carboethoxy-5-methyl furan (3) in analogy to the 3-acetyl derivatives[11].



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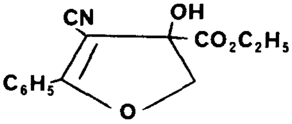
When ethyl 2-bromopyruvate is employed as an electrophile under our usual reaction conditions, 3-hydroxy-3-carboethoxy-4-cyano-5-phenyl 2,3-dihydrofuran (4) is isolated (57% yield) together with about 1% of furan (5). Dihydrofuran (4) is converted to furan (5) by dehydration with trifluoroacetic anhydride-pyridine[12] (62% yield) thus confirming the ring substitution pattern. Formation of dihydrofuran (4) involves the nucleophilic addition of the anion of (1) across the reactive carbonyl group of pyruvate followed by either direct O displacement of Br or, more likely, through the intermediacy of epoxide (6) which is formed by HBr elimination, followed by ring opening. 2-Phenyl-3-cyano-4-methyl furan has been recently reported as the product of tandem Michael-carbene insertion reaction of the benzoylacetonitrile anion (t-BuOK, THF) and propynyliodonium tetrafluoroborate (46% yield)[13].



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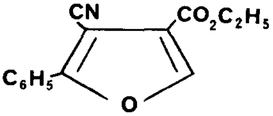

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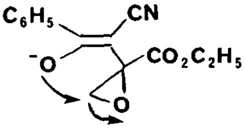

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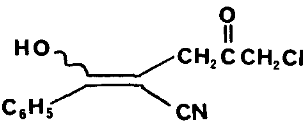
The regioselectivity of benzoylacetonitrile enolate toward attack on carbon is totally reversed with acid chlorides giving O-acylation products. Thus, pivaloyl chloride, benzoyl chloride and p-trifluoromethyl benzoyl chloride gave O-acylation products (7) (Table 1, >82% yield). Moreover, the O-acylation reaction is stereoselective favoring the E isomer as evidenced by NOE experiments on the separated regioisomers (ΔR_f=0.07, 8:1 hexanes:ethyl acetate) of (7a).

Table 1. Products from reaction of (1) with electrophiles.

Electrophile	Product	Yield (%)
$PhCOCH_2Br$	(2a) R=Ph	79
ICH_2CO_2Et	(2b) R=OEt	78
p-OMe-$PhCOCH_2Br$	(2c) R=p=OMe-Ph	63
$ClCH_2COCH_2CO_2Et$	(2d) R=CH_2CO_2Et	42
$CH_3COCHClCO_2Et$	(3)	45
$BrCH_2COCO_2Et$	(4) + (5)	58
$(CH_3)_3COCl$	(7a) R=t-Bu E:Z 61:24	85
PhCOCl	(7b) R=Ph E:Z 62:21	83
p-CF_3-PhCOCl	(7c) R=p-CF_3-Ph E:Z 51:31	82

The reaction has some limitation. The attempted reaction of (1) and 1,3-dichloroacetone proceeded sluggishly giving (8) in low yield (5%). Interestingly, (8) is the only compound in this study that was isolated as an enol[14].



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