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THE USE OF *o*-NITROARYLACETONITRILES AS CARBON ACID PARTICIPANTS IN THE MITSUNOBU REACTION

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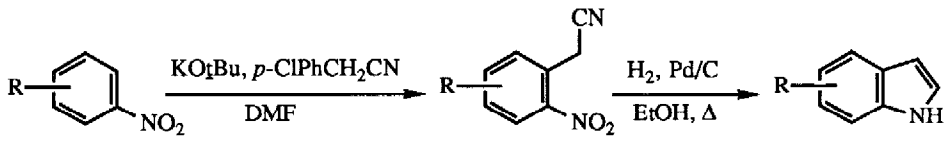
Abstract: The use of *o*-nitroarylacetonitriles as carbon acids in the Mitsunobu reaction is discussed as a method of carbon-carbon bond formation. This reaction represents a rare example of a carbon acid participating in a Mitsunobu reaction.

The Mitsunobu reaction is a powerful methodology for the formation of carbon-heteroatom bonds.[1] However, its use in the formation of carbon-carbon bonds has been limited to only a few examples.[2] This is most likely a result of the lack of carbon acids with pK_a values within the range necessary for participation in the Mitsunobu reaction ($pK_a < 14$). Also, in cases where there is a choice of reactive atom (i.e. O vs. C in 1,3-cyclohexanedione), often the Mitsunobu reaction leads preferentially to the formation of the carbon-heteroatom bond.[1] In short, the Mitsunobu reaction using carbon acid participants has barely been explored as a method for carbon-carbon bond formation.

During the course of our investigations[3] into the synthesis of novel indole derivatives as surrogates for the neurotransmitter serotonin, we examined the use of the Vicarious Nucleophic Aromatic Substitution Reaction (VNASR) as an approach to the indole heterocycle (Scheme 1).[4] Makosza has amply demonstrated this to be a worthwhile entry into substituted indole derivatives, and we wished to explore the reactivity of the various *o*-nitroarylacetonitriles (**1**) to further the scope of this methodology. The extremely deep purple color of the anion of **1** during the VNASR suggested that the pK_a of *o*-nitroarylacetonitriles (**1**)[5] might lie within the necessary range to allow for participation in the Mitsunobu reaction. Such reactivity would ultimately lead to functionalization of C3 in the final indole derivatives (Scheme 2).

Scheme 1

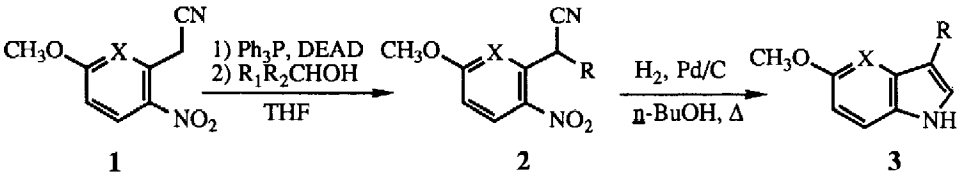


Reaction of 2-(5-methoxy-2-nitrophenyl)acetonitrile[4] with the preformed triphenylphosphine/diethyl azodicarboxylate (DEAD) complex led to an immediate formation of the deep purple color indicative of the formation of the anion of acetonitrile (**1**). This was taken as an indication that the triphenylphosphine/DEAD complex created an environment of sufficient basic nature to deprotonate the acetonitrile (**1a**, X=C). Treatment of this mixture with benzyl alcohol caused a rapid (i.e. within minutes) disappearance of the anionic purple color, and led to the formation of the desired 2-benzylacetonitrile (**2a**) in 70% yield.[6] A number of other alcohols were then subjected to these conditions, and the results of this study are tabulated in Scheme 2. Also, 2-(6-methoxy-3-nitropyrid-2-yl)acetonitrile (**1b**, X=N) was successfully used as the carbon acid participant in these Mitsunobu reactions. The conversion of a few of the substituted acetonitriles (**2**) to their corresponding indoles (**3**) was effected using hydrogenation of **2** at 80 °C using 10% Pd/C (15 - 20% by weight).

While it was apparent that the reaction of *o*-nitroarylacetonitriles (**1**) with alcohols to yield **2** under Mitsunobu conditions was general, a number of important observations were also made. For example, reversing the order of addition in this reaction, i.e. adding the acetonitrile (**1a**, X=C) to a mixture of triphenylphosphine/DEAD/benzyl alcohol, led to a markedly slower appearance and disappearance of the anionic purple color, but in the end led to an equivalent yield of the desired product (**2a**). We concluded from this that the triphenylphosphine/DEAD complex must be coordinated with the alcohol oxygen in some way when the alcohol is introduced into the reaction prior to the arylacetonitrile (**1**). Also, the rate of reactivity[7] of these different alcohols (and the yield of product [**2**]) seemed to follow

an S_N2 pattern of relative reactivity (i.e. $PhCH_2$ = propargyl > allyl >> methyl >> propyl> cyclohexyl). Since the reaction of simple alkyl alcohols was particularly slow (i.e. 24-72 hours), it was not surprising that the phthalimidoethanol gave only a trace of product after three days (as seen by ^1H NMR spectroscopy). Heating these reactions had no effect on the yield or course of reaction.

Scheme 2



1 2 3

	X	R	% Yield of 2	% Yield of 3
a)	C	CH_2Ph	70	54
b)	C	CH_2-*p*-Ph-OCH_3	59	50
c)	C	CH_2-*p*-Ph-NO_2	51	--
d)	C	CH_3	45	--
e)	N	CH_3	66	16
f)	C	$CH_2CH{=}CH_2$	70	--
g)	C	$CH_2C{\equiv}CH$	56	41 [as **3i**]
h)	N	$CH_2C{\equiv}CH$	76	--
i)	C	$CH_2CH_2CH_3$	72	42
j)	C	CH_2CH_2Phthalimide	trace	--
k)	N	CH_2CH_2Phthalimide	trace	--
l)	C		27	--
m)	N		35	--

A general procedure for these Mitsunobu reactions is as follows. To a stirred solution of triphenylphosphine (3.00 mmol, 1.5 eq) and diethyl azodicarboxylate (3.00 mmol, 1.5 eq) in anhydrous tetrahydrofuran (15 mL) at 0 °C under nitrogen was added the *o*-nitroarylacetonitrile (**1**, 2.00 mmol) directly as a solid. The reaction solution immediately became extremely deep purple in color. The alcohol (3.00 mmol, 1.5 eq) was then added (dropwise if liquid, portionwise if solid), and the resulting reaction solution was stirred at room temperature under nitrogen until all evidence of

purple color was gone from the reaction (less than 5 min to 72 hours depending on substrate). The reaction solution (usually pale brown in color) was then evaporated under reduced pressure, and the residue column chromatographed to afford the desired substituted acetonitrile (**2**).

In conclusion, these *o*-nitroarylacetonitriles (**1**) are carbon acid participants in the Mitsunobu reaction with a variety of alcohols. Additionally, these acidic acetonitrile derivatives appear to be useful as acid/base "indicators" for the course of these reactions. We are presently exploring the use of **1** as mechanistic probes to further our understanding of the Mitsunobu reaction and will report those results shortly.

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2. To our knowledge, there has been only one published report of carbon acids participating in a Mitsunobu reaction: Wada, M. and Mitsunobu, O. Tetrahedron Letters, **1972**, 1279.
3. a) Macor, J.E.; Burkhart, C.A.; Heym, J.H.; Ives, J.L.; Lebel, L.A.; Newman, M.E.; Nielsen, J.A.; Ryan, K. Schulz, D.W.; Torgersen, L.K.; and Koe, B.K. J. Med. Chem., **1990**, 33, 2087; b) Macor, J.E. and Newman, M.E. Heterocycles, **1990**, 31, 805.
4. Makosza, M.; Danikiewicz, W. and Wojciechowski, K. Liebigs. Ann. Chem., **1988**, 203.
5. The pK_a of **1a** was determined via a spectrophometrically monitored titration. Over four separate experiments the pK_a determined to be 13.1±0.1 in 1:1 acetonitrile/water.
6. All new compounds disclosed in this communication have been thoroughly characterized including ^1H NMR, ^{13}C NMR, IR, LRMS, HRMS and/or elemental analysis.
7. The rate of the visually observed disappearance of the anionic purple color in these reactions can be used as a direct measure of the relative rate of the desired Mitsunobu reaction.

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