THE USE OF *o*-NITROARYLACETONITRILES IN THE MITSUNOBU REACTION: MECHANISTIC IMPLICATIONS AND SYNTHETIC APPLICATIONS

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Abstract - *o*-Nitroarylacetonitriles (**1**) have been used as carbon acid participants in the Mitsunobu reaction to yield 2-(*o*-nitroaryl)-2-alkylacetonitriles (**2**). Reductive cyclization of **2** afforded 3-alkylindoles (**3**) in moderate yield. The use of *o*-nitroarylacetonitriles (**1**) as acid/base indicators and mechanistic probes in the Mitsunobu reaction in conjunction with results from other studies have led to the following hypotheses concerning the mechanism of that reaction: 1) the nature of the acid participant in a Mitsunobu reaction determines the mechanistic course of the reaction; and 2) carbon acid participants react via an "outer sphere" second order process whose rate is heavily dependent on the nature of the alcohol used; 3) heteroatom acid participants (i.e. -OH and -NH-) having high affinity for phosphorus utilize an "inner sphere" first order process which does not depend heavily on the nature of the alcohol used; and 4) the order of reactant addition can have significant effects on the reaction rate and success, and optimal reaction results occur with the addition of the alcohol last to a solution of DEAD/Ph_3P/acid participant.

INTRODUCTION

The Mitsunobu reaction[1] is a well utilized and well studied process in synthetic organic chemistry. However, despite its widespread use, the mechanistic details of the reaction process are still a subject of considerable debate. Phosphorous nmr, ^{18}O labelling, and numerous kinetic studies have been brought to bear on the mechanism of this reaction, but its secrets still remain elusive, and further tools are needed to finally lay bare the pathway of this process.

To further complicate these matters, it appears that more than one mechanism may be operating, depending

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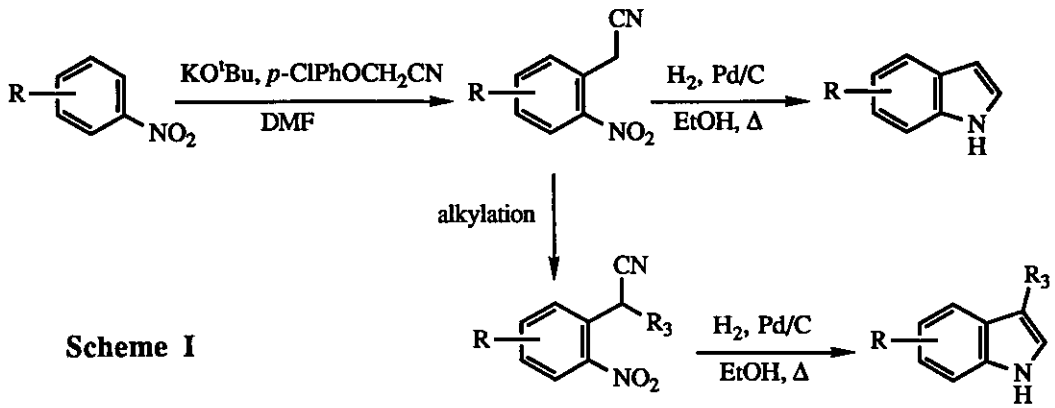
This paper is sincerely dedicated to Professor E. C. Taylor on the occasion of his seventieth birthday.

on the order of addition and type of the reaction substrates. In the "classical" Mitsunobu reaction, the diazodicarboxylate (i.e. DEAD) is added last to a solution of triphenylphosphine/acidic component (i.e. a carboxylic acid)/alcohol. Modifications of this procedure include preforming the DEAD/triphenylphosphine adduct before the addition of either the acidic component or the alcohol. It has been suggested that, depending on the order of reactant addition, different intermediates and reaction rates may be seen in the reaction process.[1,2]



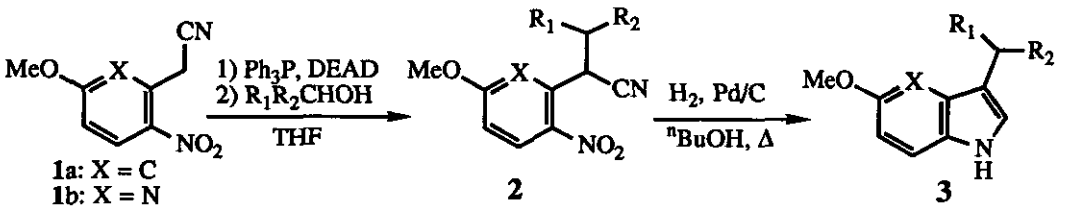
Scheme I

During the course of investigations in our laboratory concerning the synthesis of indole derivatives, we explored the use of *o*-nitroarylacetonitriles (1) as precursors to indole derivatives.[3] The compounds (1) were readily available via a Vicarious Nucleophilic Aromatic Substitution Reaction[4] on substituted nitrobenzenes, and reductive cyclization of these molecules yielded the appropriate indoles. Since the resulting methylene on the acetonitrile (**1a**) was found to very acidic with a pKa of 13.1, we envisioned that appropriate substitution on this active methylene would ultimately lead to 3-substituted indoles (Scheme I). The resulting highly stabilized anion of **1** is deep purple in color and unmistakable, and formation of this anion can be achieved readily with a number of bases. Since the methylene in **1a** was relatively acidic, we attempted to alkylate this methylene using a Mitsunobu reaction. Addition of **1a** to a preformed solution of Ph_3P/DEAD resulting in an immediate formation of the intense purple color indicative of anion formation. Quenching this reaction solution with benzyl alcohol led to a rapid (less than five minutes) disappearance of the anionic purple color. Upon reaction work-up, a 70% yield of the 2-benzylacetonitrile (**2a**, Scheme II) was isolated. From this reaction we became aware of the usefulness of **1** as an acid/base indicator for the course of a Mitsunobu reaction, and this report details the results of our mechanistic investigations and conclusions.

RESULTS AND DISCUSSION

Reports on the use of active methylene compounds as the acid participant in a Mitsunobu reaction are very limited, and this type of Mitsunobu reaction has only appeared in the original review of the reaction. The lack of appropriate carbon acids with pK_a values within the range necessary for participation in the Mitsunobu

Scheme II



1a: X = C
1b: X = N

2

3

	X	R_1	R_2	% Yield of 2	Reaction Time (min)	% Yield of 3
a)	C	-Ph	-H	70	5	54
b)	C	-*p*-PhOMe	-H	59	3	50
c)	C	-*p*-$PhNO_2$	-H	51	17	--
d)	C	-Ph	-CH_3 (R)	48 [a]	7	42
e)	C	-Ph	-CH_3 (S)	56 [a]	6	58
f)	C	-H	-H	45	240	--
g)	N	-H	-H	66	34	16
h)	C	-CH=CH_2	-H	70	13	--
i)	C	-C≡CH	-H	56	0.5	41 [as 3k]
j)	N	-C≡CH	-H	76	9	--
k)	C	-CH_2CH_3	-H	72	1440	42
l)	C	-CH_2Phthalimide	-H	trace	4500	--
m)	N	-CH_2Phthalimide	-H	trace	4500	--
n)	C	-$CH_2CH_2CH_2CH_2CH_2$-		27	4300	--
o)	N	-$CH_2CH_2CH_2CH_2CH_2$-		35	1440	--

[a] as a mixture of epimers

reaction (pK_a approximately < 14) has certainly contributed to the paucity of examples, and when there is a choice between a carbon or heteroatom as the reacting center (i.e. in 1,2-cyclohexanedione), the process favors reaction at the heteroatom. Therefore, the utility of the Mitsunobu reaction to form carbon-carbon bonds has not as yet been fully examined.

Reaction of nitroaryls with *p*-chlorophenoxyacetonitrile under basic conditions leads to the incorporation of -CH_2CN ortho to the nitro group in the aromatic ring (Scheme I).[2] The methylene now contained in the resulting *o*-nitroarylacetonitriles (**1**) is very acidic as a result of the ability of the molecule to broadly disperse the electron density from the resulting conjugate through resonance stabilization. Not surprisingly, this highly stabilized anion of **1** is deep purple in color, and **1** functions as an acid/base indicator, depending on the pH of the solution. Accordingly, the pK_a of **1a** (X =C) was determined to be 13.1±0.1 (n=4) in a water/acetonitrile [1:1] solution using a spectrophotometric titration.

Since addition of **1a** (X =C) to a solution of DEAD/Ph_3P resulted in the immediate formation of the intense purple color indicative of the anion of **1a**, it can be concluded that the basicity of the DEAD/Ph_3P complex is of

sufficient strength to apparently fully deprotonate an acid of pK_a 13. This result represents an excellent quantification of the basicity of the DEAD/Ph_3P complex. Addition of various alcohols to the purple solution of **1**/DEAD/Ph_3P led to a disappearance of the purple color (usually to a yellow/brown solution) forming the alkylated derivatives (**2**, Scheme II). Reductive cyclization of **2** allowed for the formation of the desired 3-substituted indoles (**3**), although the yields of this reaction varied from poor to moderate. The temperature needed to effect this cyclization (80 °C) was higher than previously reported for unsubstituted arylacetonitriles,[2] and it would appear that this higher reaction temperature was deleterious to the efficiency of the process. However, because the C3-alkylation of indoles is often complicated by undesired N-alkylation, this type of synthesis represents a significant, unambiguous and simple approach to 3-substituted indole and azaindole derivatives. Optimization of the reductive cyclization route would further the utility of this process.

Both the yield of **2** and the time required to visually see the anionic purple color disappear was highly dependent on the nature of the alcohol used in the reaction (Scheme II). Use of benzyl alcohols, propargyl alcohol, and allyl alcohol resulted in rapid disappearance of the anionic color and good yields of **2**. Use of methanol, propanol, and cyclohexanol resulted in a much slower disappearance of the purple color and lower yields of **2**. Using the visual disappearance of color as the measure of reaction rate, the order of alcohols from fastest to slowest would be: propargyl > *p*-methoxybenzyl ≈ benzyl > allyl ≈ *p*-nitrobenzyl > methyl >> propyl > cyclohexyl >>> phthalimidylethyl. This order of reactivity is reminiscent of the order of reactivity of substrate structure in a classical S_n2 reaction.[5] These results would suggest that these Mitsunobu reaction using the carbon acids (**1**) proceed via an S_n2-like reaction process where the nature of the substituent has a great deal of effect on the rate and efficiency of the reaction. This result, however, is in contrast to the Mitsunobu reactions involving heteroatom acids, such as carboxylic acids, phenols, or phthalimide. In these reactions, the reaction rate appears to be generally unaffected by the nature of the alcohol used.[1] This would seem to suggest that at least two different mechanistic pathways are available in the Mitsunobu reaction.

Reaction of **1a** (X =C) with either R-(+)- or S-(-)-*sec*-phenethyl alcohol gave a mixture of two epimers which could be separated by column chromatography. Using S-(-)-*sec*-phenethyl alcohol, the less polar epimer had a specific rotation of +15° while the more polar epimer had a specific rotation of -115°. Using R-(+)-*sec*-phenethyl alcohol, the less polar epimer had a specific rotation of -13° while the more polar epimer had a specific rotation of +117°. The equal, but opposite specific rotations of the two less polar and two more polar epimers from these reactions suggest that these Mitsunobu reactions proceeded with stereogenic integrity. Reduction of the epimeric mixture of **2d** lead to the enantiomeric indole (**3d**) (derived from R-(+)-*sec*-phenethyl alcohol) whose specific rotation (-54°) was equal, but opposite to the specific rotation (+59°) of indole (**3e**) (derived from S-(-)-*sec*-phenethyl alcohol). The stereogenic centers contained in these indoles originated in the chiral alcohols, and these results suggest that the Mitsunobu reaction occurred with complete inversion of absolute configuration consistent with literature precedents.

The use of 1,2-propanediol as the alcohol for condensation with **1a** (X =C) gave interesting results, namely an almost immediate disappearance of the anionic purple color, but the formation of no expected product, and almost quantitative return of **1a**. Somehow during the rapid course of that particular reaction, protonation of

the anion of **1a** (formed via the DEAD/Ph_3P complex) occurred preferential to Mitsunobu coupling. Addition of external base (i.e. NaH) at this point in the reaction led to the formation of the anionic purple color, but no coupling product was seen after three days, and the purple color persisted.

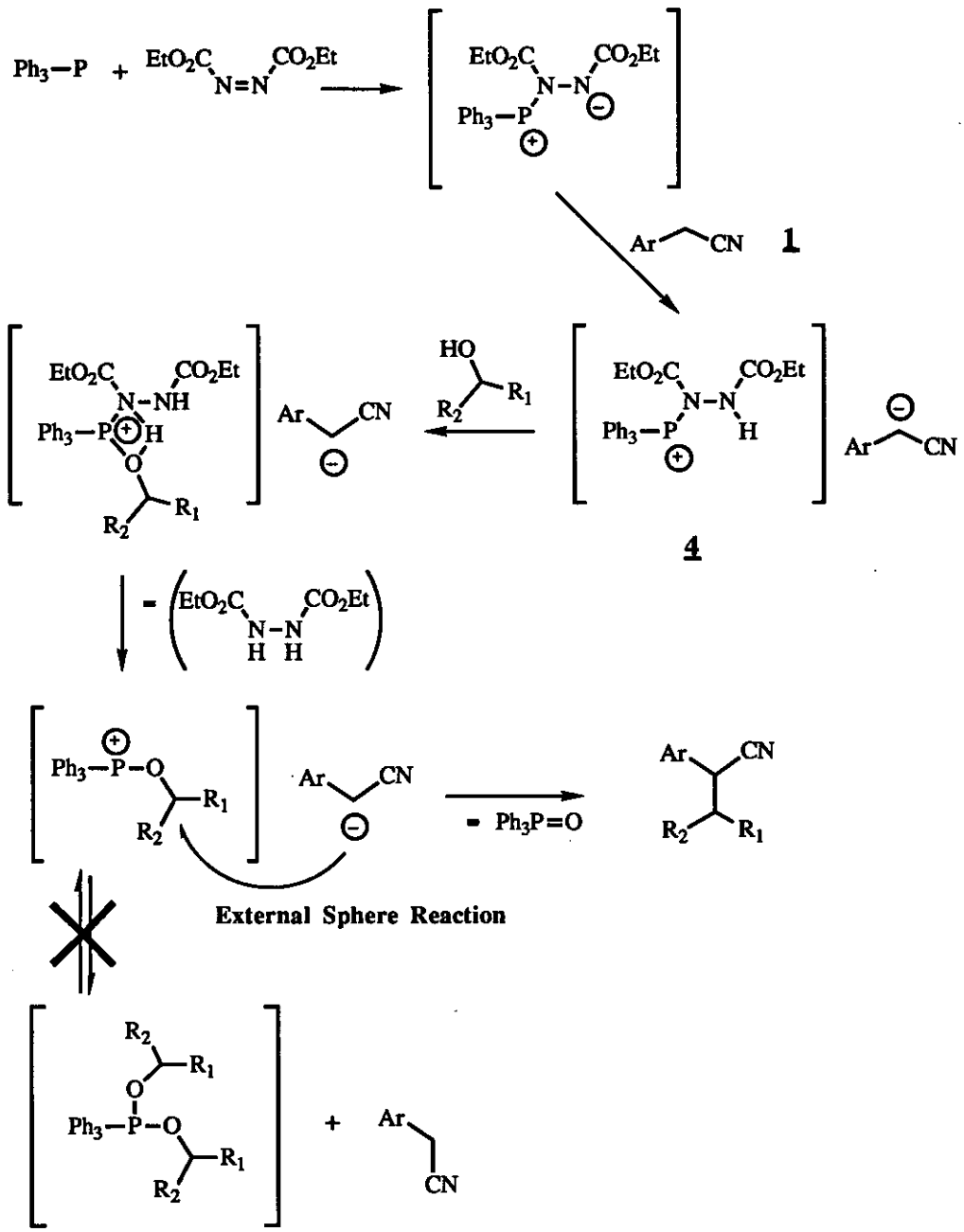
These results along with evidence from previous studies suggest the following hypotheses: 1) the nature of the acid participant in a Mitsunobu reaction determines the mechanistic course of the reaction; and 2) carbon acid participants react via an "outer sphere" second order process whose rate is heavily dependent on the nature of the alcohol used; 3) heteroatom acid participants (i.e. -OH and -NH-) having high affinity for phosphorus react via an "inner sphere" first order process which does not depend heavily on the nature of the alcohol used; and 4) the order of reactant addition can have significant effects on the reaction rate and success.

Scheme III details our hypothesized course of a Mitsunobu reaction using a carbon acid such as **1a**. Formation of the DEAD/Ph_3P complex is almost immediate upon mixing, creating a species of sufficient basicity that deprotonation of **1** occurs upon dissolution. This protonation of the DEAD/Ph_3P complex has often been overlooked in mechanistic studies of the Mitsunobu reaction, *but proton transfer to the DEAD/Ph_3P complex is, in fact, the key to the oxidation of the phosphorus in the complex.* Once the DEAD/Ph_3P complex has been protonated to form the cation (**4**), the pair of electrons which were donated in the complex by the phosphorus have now been lost to the more electronegative nitrogen atom, thus creating a formally positively charged and formally oxidized phosphorus atom. The course of the Mitsunobu reaction is "downhill" from this point.[6] While one could argue that the reaction is still reversible at this point [i.e. that there is an equilibrium between the DEAD/Ph_3P complex and its protonated, oxidized form (**4**)], the intense purple color of the anion of **1** in the reaction solution and electronegativities suggest that any equilibrium at this point significantly favors the formation of **4**. Up to this point in the reaction sequence, **1** has functioned only as proton source, and it is reasonable to assume that the only critical characteristic of any proton source needed to form(**4**)is pK_a. Therefore, this rapid, arguably irreversible formation of **4** can be seen as universal to any Mitsunobu reaction where the acid source (i.e. **1**, or phthalimide or a carboxylic acid) is added to the DEAD/Ph_3P complex before the alcohol. Since the affinity of soft carbon anions to phosphorus is not significantly strong, we see the anion of **1** acting simply as an external, negatively charged counterion to **4**.

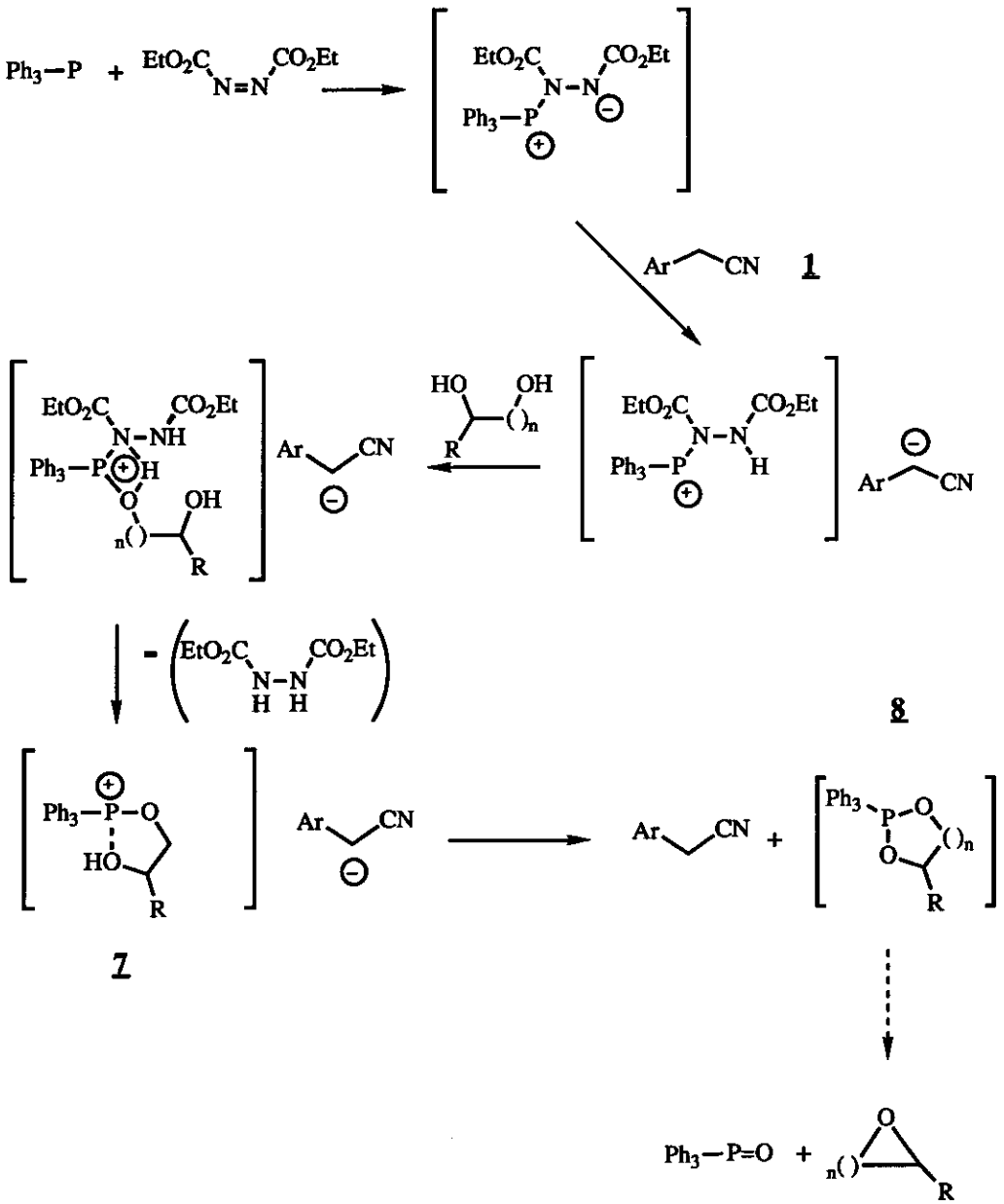
Addition of the alcohol to the reaction solution containing the protonated DEAD/Ph_3P complex (**4**) should lead to rapid coordination of the alcohol oxygen with the positively charged phosphorus, followed by the expulsion of the 1,2-dicarbethoxyhydrazine (reduced DEAD), protonated by the alcohol proton. When 1-propanol was used, a ^1H nmr of the purple reaction solution (i.e. indicating little to no reaction) was taken immediately upon the addition of the alcohol. This nmr spectrum of the DEAD/Ph_3P/**1a**/propanol mixture (using $CDCl_3$ as reaction solvent) indicated almost complete formation of reduced DEAD immediately after the addition of the alcohol [as seen by the chemical shift of ethoxy group in reduced DEAD versus DEAD]. No resonances were identified for **2k**, indicating that no detectable product (**2k**) had formed yet. Expulsion of reduced DEAD would lead to the phosphonium cation (**5**), which has been previously postulated by many studies. The phosphonium cation (**5**) is now the substrate for backside external S_n2 by the anion of **1**, leading to the formation of **2** and the expulsion of triphenylphosphine oxide. It is important to note that the formation of the phosphorane species

Scheme III

Mitsunobu Reaction with Carbon Acid

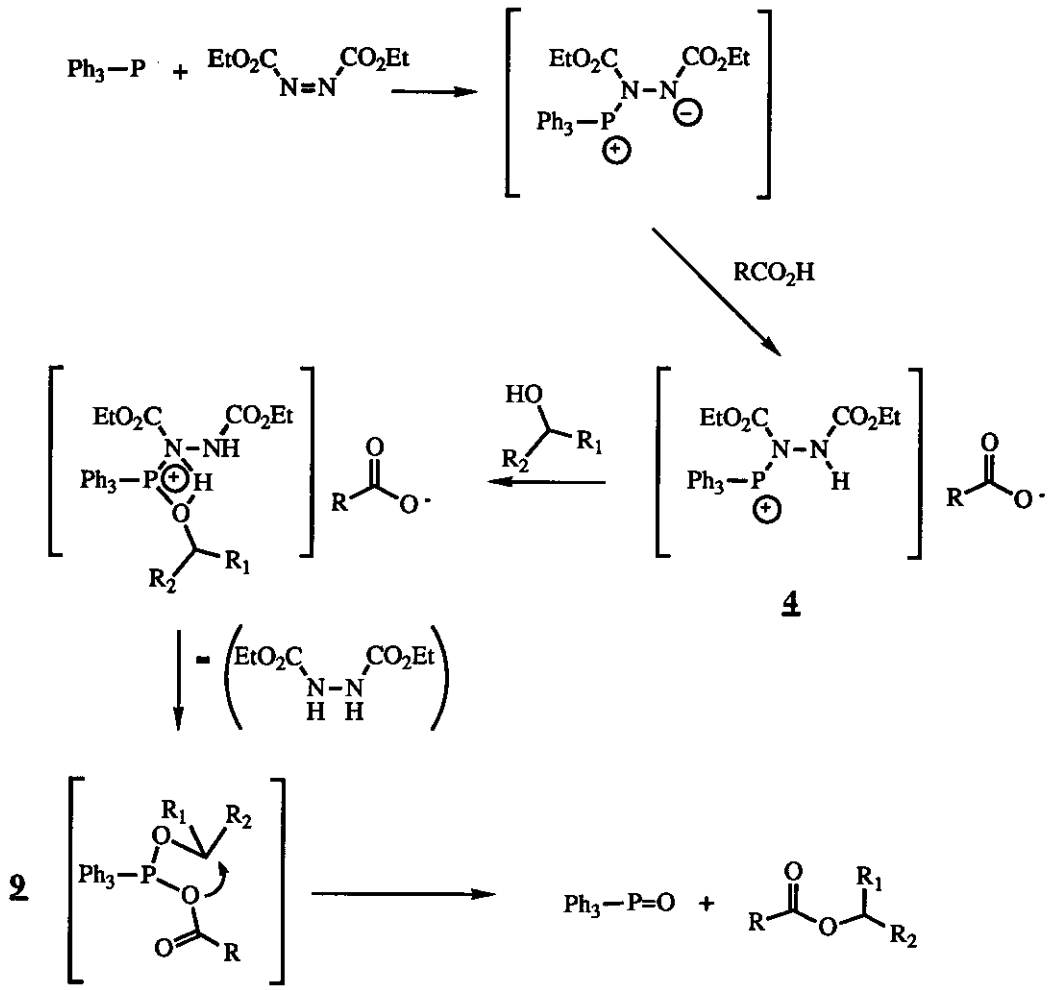


Scheme IV - Failure of Diol



Scheme V

Mitsunobu Reaction with Heteroatom Acid



Internal Sphere Reaction

(6) can be excluded from this reaction mechanism for the following reason: the formation of **6** would necessarily protonate the anion of **1** leading to the return of **1** and loss of the anionic purple color with no formation of **2**. The decomposition of **6** to **5**, reforming the anion of **1** seems unlikely based on

electronegativity and pK_a considerations. Therefore, when the acid participant is added to a solution containing the DEAD/Ph_3P complex *before the addition of any alcohol*, then upon the addition of alcohol, little if any of the phosphorane (**6**) forms.

However, when 1,2-propanediol was used in place of the alcohol in this Mitsunobu reaction, protonation of the anion of **1** was the outcome of that reaction (Scheme IV). No coupled product (**2**) was isolated. The hypothesized mechanism of that reaction is drawn in Scheme IV. As before, reaction of **1** with the DEAD/Ph_3P complex forms the protonated complex (**4**) and the anion of **1**. Addition of 1,2-propanediol to this reaction solution should initially follow the same course as depicted in Scheme III. Formation of the phosphonium cation (**7**) would be analogous to **5** in Scheme III. However, **7** contains an additional *intramolecular* alcohol. Driven by entropic considerations and its affinity for oxidized phosphorus, the second alcohol formally bonds to the phosphorus, and the cationic charge is removed by the loss of its proton, which is captured by the anion of **1**, thus quenching the nucleophile and leading to the rapid loss of anionic color, as observed in this particular reaction. The intramolecular availability of the second alcohol in this reaction creates the proper scenario where the phosphorane (**8**) can be formed. The fate of **8** has not been determined by us, but formation of ethers using DEAD/Ph_3P suggests that epoxide formation is likely. The formation of the phosphorane (**6**) in Scheme III is slow because of the intermolecular nature of its formation. Only when the formation of **2** is very slow might the formation of **6** occur to any significant degree. This would be the case when poor alcohol substrates were used in these Mitsunobu reactions (i.e. phthalimidylethanol), since over days the anionic purple color would slowly disappear, but no significant amount of coupled product would be seen.

Therefore, the phosphonium cation (**5**) in Scheme III is the reactive species in this reaction. The attack of the anion of **1** on **5** occurs external to the sphere of the phosphorus atom. That is, the anion of **1** is not coordinated to the phosphorus atom in **5**, and attack of this relatively nucleophilic anion on the carbon atom α to the oxygen atom occurs intermolecularly. The dramatic effect of the nature of the alcohol on the rate of these reactions supports this interpretation. That is, the rate of these Mitsunobu reactions is determined by the S_n2 reactivity of the substrate alcohol, i.e. benzyl > primary alkyl > secondary alkyl. This reaction fails for any alcohol which would be a poor S_n2 substrate. *Therefore, the use of carbon acid participants in the Mitsunobu reaction is limited in its scope by simple S_n2 considerations*: reactivity of the alcohol substrate and steric bulk around the alcohol oxygen. This would explain the lack of use of this reaction, since few carbon acids lie in the correct pK_a range to be deprotonated by the DEAD/Ph_3P complex and the choice of reactive alcohols is small. These results, however, might predict that a more electron poor triphenylphosphine molecule [i.e. (p-NO_2-Ph)$_3$P] could improve the scope of this particular use of the Mitsunobu reaction by creating a more reactive alcohol/phosphorus complex.

In contrast to a Mitsunobu reaction using a carbon acid participant (Scheme III), the nature of the alcohol component in a Mitsunobu reaction using a carboxylic acid, a phenol, or phthalimide has much less effect on the rate or course of the reaction. Furthermore, the esterification of benzoic acid using DEAD/Ph_3P and 1,2-propanediol is successful, affording the more hindered ester.[7] The degree of nucleophilicity of a carboxylate anion is poor, and one would not imagine a carboxylate anion to be a good S_n2 nucleophile. Thus, the Mitsunobu

reaction which effects esterification of carboxylic acids would appear to proceed via a mechanism which is different from that shown in Scheme III for carbon acids. This might also be the case with all heteroatom acid participants in a Mitsunobu reaction. Scheme V presents an alternate mechanism for the Mitsunobu reaction using heteroatom acid participants, exemplified using the esterification of a carboxylic acid. Addition of a carboxylic acid to a solution of the DEAD/Ph_3P complex should result in an acid/base reaction analogous to Scheme III forming the protonated DEAD/Ph_3P complex (4) and the carboxylate anion. Addition of the alcohol component to this reaction would similarly proceed to the formation of the phosphonium cation (5) with the carboxylate as the counterion and loss of reduced DEAD. Whereas, the affinity of a carbon anion of 1 for the phosphorus atom in 5 would be poor, and the intermolecular addition of another alcohol molecule is not favored, the affinity of the carboxylate anion and its negatively charged oxygen atom for phosphorus would be significant, leading to the phosphorane (9). Intramolecular decomposition of 9, possibly via a betaine-like intermediate reminiscent of a Wittig reaction, would lead to the ester and triphenylphosphine oxide. The P-O bond strengths would direct which P-O bond was broken and which was retained. As a result of inductive effects, one would expect that the P-O bond from the carboxylate would be weaker than the P-O bond from the alcohol. The geometry of attack from this intermediate (9) would necessitate backside S_n2-like bond formation with inversion of configuration at the carbon atom bearing the alcohol oxygen. The intramolecular or "inner sphere" nature of this reaction would predict that the reaction rate would be little effected by the nature of the alcohol. These predictions are in accord with our mechanism, and this hypothesized mechanism is consistent with results from previous mechanistic studies of the Mitsunobu reaction.

These results do not address the consequences of a different order of addition in the Mitsunobu reaction. A different set of intermediates are certainly possible, and in the absence of the acid participant, the formation of the phosphorane (6) occurs rapidly.[8] The conclusion of the Mitsunobu reaction from this point does occur, but the mechanism of that particular reaction pathway cannot be addressed using 1.

The results of this study indicate the importance of the protonation of the DEAD/Ph_3P complex in the Mitsunobu reaction. *Protonation of the DEAD/Ph_3P complex can be viewed as the oxidation/reduction step in the mechanism of the Mitsunobu reaction.* Protonation of the nitrogen atom in DEAD leaves a N-P bond in which the bulk of the electron density (based on electronegativity considerations) would reside on the nitrogen atom, leaving the phosphorus atom positively charged (oxidized). Therefore, it would appear that the best method of addition of reactants in a Mitsunobu reaction would be as described in this paper: 1) formation of the DEAD/Ph_3P complex, 2) addition of the acid participant to protonate the complex, which effectively is the oxidation/reduction step in the sequence, and 3) add the alcohol to this solution of protonated DEAD/Ph_3P complex and deprotonated acid participant. This method of addition reduces the possibility of unwanted interactions and/or equilibrium reactions between the phosphorus in the DEAD/Ph_3P complex and the alcohol. Protonation of the DEAD/Ph_3P complex with the acid participant "cocks" the reaction gun which is fired upon the addition of the alcohol.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover open capillary melting point apparatus and are uncorrected. Infrared spectra were obtained from a Perkin Elmer ir-283B Infrared Spectrophotometer, and nmr spectra were recorded on either a Bruker AM-300 (300 MHz), Varian XL300 (300 MHz), or Varian XL250 (250 MHz) spectrometer. Nmr data are reported in parts per million (δ) and are referenced to the deuterium lock signal from the sample solvent. Low resolution mass spectra were obtained on a Finnigan 4310 instrument; high resolution mass spectra (EI and FAB) were obtained on a Kratos Concept IS instrument. Elemental analyses were performed at Central Research Division, Pfizer Inc., Groton, CT.

Commercial reagents (Aldrich Chemical Co.) were utilized without further purification, including Aldrich anhydrous solvents. Diethyl ether was dried via distillation over sodium hydride. 2-(2-Nitro-5-methoxyphenyl)acetonitrile and 2-(3-nitro-6-methoxypyrid-2-yl)acetonitrile were synthesized as previously described.[4] Chromatography refers to column chromatography performed using 32-63 μm silica gel (approx 50 g silica gel per gram of material to be chromatographed) and executed under nitrogen pressure (flash chromatography) conditions. Room temperature (rt) refers to 20 - 25° C. All optical rotations were recorded using a sodium (589 nm) lamp.

General Synthesis of 2-Alkyl-2-(2-nitro-5-methoxyaryl)acetonitriles (2).

To a stirred solution of triphenylphosphine (0.79 g, 3.01 mmol, 1.5 eq.) in anhydrous THF (10 ml) at 0 °C was added DEAD (0.47 ml, 2.98 mmol, 1.5 eq.). The resultant yellow reaction solution was stirred at 0 °C under nitrogen for 10 min. Then either 2-(2-nitro-5-methoxyphenyl)acetonitrile (0.38 g, 1.98 mmol) or 2-(3-nitro-6-methoxypyrid-2-yl)acetonitrile (0.39 g, 2.02 mmol) was added as a solid rapidly, and the resulting deep purple colored reaction solution was stirred at 0 °C under nitrogen for 5 min. Then, the desired alcohol (3.00 mmol) was added directly either as a liquid or solid, and the resulting reaction solution was stirred at 0 °C under nitrogen for 0.5 min to 72 h depending on the alcohol. Completion of the reaction was determined by the disappearance of the purple color and by tlc. The resulting solution was then evaporated under reduced pressure, and the residual oil directly chromatographed using silica gel (approx 100 g) and eluting with an appropriate solvent system to afford the desired title compound.

2-(5-Methoxy-2-nitrophenyl)-3-phenylpropionitrile (2a).

2-(2-Nitro-5-methoxyphenyl)acetonitrile and benzyl alcohol were used, and chromatography using 1:4 ethyl acetate/hexanes afforded **2a** (70%) as a pale yellow solid: mp 106.0-108.8 °C; ir (KBr) 2245, 1610, 1595, 1520, 1465, 1455, 1345 cm^{-1}; ^1H nmr ($CDCl_3$) δ 8.19 (d, J=9.2 Hz, 1H), 7.37-7.26 (m, 5H), 7.08 (d, J=2.7 Hz, 1H), 6.96 (dd, J=9.2 and 2.7 Hz, 1H), 5.17 (dd, J=9.3 and 4.4 Hz, 1H), 3.88 (s, 3H), 3.35 (dd, J=13.4 and 4.4 Hz, 1H), 3.07 (dd, J=13.4 and 9.3 Hz, 1H); ^{13}C nmr ($CDCl_3$) δ 163.8, 140.0, 135.7, 133.6, 129.4, 128.8, 128.6, 127.7, 119.7, 115.4, 114.4, 56.1, 41.2, 36.9; ms (m/z, relative intensity) 282 (M^+, 3), 265 (7), 176 (56), 91 (100). Anal. Calcd for $C_{16}H_{14}N_2O_3$: C, 68.08; H, 5.00; N, 9.92. Found: C, 68.08; H, 4.79; N, 9.75.

2-(5-Methoxy-2-nitrophenyl)-3-(4-methoxyphenyl)propionitrile (2b).

2-(2-Nitro-5-methoxyphenyl)acetonitrile and 4-methoxybenzyl alcohol were used, and chromatography using 2:3 ether/hexanes afforded **2b** (59%) as a pale orange solid: mp 119.0-125.0 °C; ir (KBr) 2245, 1615, 1580, 1520, 1490, 1460 cm^{-1}; ^1H nmr ($CDCl_3$) δ 8.19 (d, J=9.2 Hz, 1H), 7.25-7.19 (m, 2H), 7.09 (d, J=2.7 Hz, 1H), 6.96 (dd, J=9.2 and 2.7 Hz, 1H), 6.91-6.85 (m, 2H), 5.11 (dd, J=9.2 and 4.4 Hz, 1H), 3.89 (s, 3H), 3.81 (s, 3H), 3.28 (dd, J=13.5 and 4.3 Hz, 1H), 3.00 (dd, J=13.5 and 9.3 Hz, 1H); ^{13}C nmr ($CDCl_3$) δ 163.8, 159.2, 140.2, 133.7, 130.5, 128.6, 127.8, 119.8, 115.4, 114.2, 114.1, 56.1, 55.3, 40.5, 37.2; ms (m/z, relative intensity) 312 (M^+, 8), 184 (5), 135 (6), 121 (100). Anal. Calcd for $C_{17}H_{16}N_2O_4$: C, 65.38; H, 5.16; N, 8.97. Found: C, 65.69; H, 5.36; N, 8.69.

2-(5-Methoxy-2-nitrophenyl)-3-(4-nitrophenyl)propionitrile (2c).

2-(2-Nitro-5-methoxyphenyl)acetonitrile and 4-nitrobenzyl alcohol were used, and chromatography using 5:4:1 petroleum ether/methylene chloride/acetone afforded **2c** (51%) as a pale yellow solid: mp 154.5-158.5 °C; ir (KBr) 2240, 1615, 1610, 1580, 1520, 1340, 1295 cm^{-1}; ^1H nmr ($CDCl_3$) δ 8.27-8.21 (m, 3H), 7.53 (d, J=8.7 Hz, 1H), 7.16 (d, J=2.7 Hz, 1H), 7.01 (dd, J=9.2 and 2.7 Hz, 1H), 5.17 (dd, J=9.8 and 4.1 Hz, 1H), 3.93 (s, 3H), 3.46 (dd, J=13.4 and 4.1 Hz, 1H), 3.16 (dd, J=13.4 and 9.8 Hz, 1H); ^{13}C nmr ($CDCl_3$) δ 164.1, 147.8, 143.2, 139.8, 132.9, 130.4, 129.1, 124.0, 119.0, 115.7, 114.2, 56.3, 40.8, 36.7; ms (m/z, relative intensity) 327 (M^+, 4), 310 (11), 191 (28), 175 (44), 149 (43), 135 (100), 106 (81). Anal. Calcd for $C_{16}H_{13}N_3O_5$: C, 58.72; H, 4.00; N, 12.84. Found: C, 58.76; H, 3.96; N, 12.51.

2-(R,S)-(5-Methoxy-2-nitrophenyl)-3-(R)-methyl-3-phenylpropionitrile (2d).

2-(2-Nitro-5-methoxyphenyl)acetonitrile and S-(-)-*sec*-phenethyl alcohol were used, and chromatography using 1:3 ethyl acetate/hexanes afforded **2d** (48%) as a 2:3 mixture of diastereomers (less polar:most polar). The first (less polar) diastereomer eluted was a yellow solid: mp, 110.0-112.0 °C; ir (KBr) 2235, 1600, 1585, 1515, 1505, 1330 cm^{-1}; ^1H nmr ($CDCl_3$) δ 8.15 (d, J=9.2 Hz, 1H), 7.28-7.24 (m, 3H), 7.07-7.03 (m, 2H), 6.87 (dd, J=9.2 and 2.8 Hz, 1H), 6.33 (d, J=2.7 Hz, 1H), 5.29 (d, J=5.0 Hz, 1H), 3.59 (s, 3H), 3.41-3.29 (m, 1H), 1.64 (d, J=7.1 Hz, 3H); ^{13}C nmr ($CDCl_3$) δ 163.0, 140.3, 139.5, 132.9, 128.4, 128.3, 128.1, 127.7, 118.9, 115.2, 115.1, 55.8, 43.8, 41.7, 19.4; ms (m/z, relative intensity) 296 (M^+, 9), 192 (9), 105 (100); $[\alpha]^{25}$ = +15° (c=1, $CHCl_3$). Anal. Calcd for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.44; N, 9.45. Found: C, 68.76; H, 5.20; N, 9.10.

Further elution afforded the second (more polar) diastereomer as a yellow oil: Ir ($CHCl_3$) 2235, 1603, 1582, 1339, 1295 cm^{-1}; ^1H nmr ($CDCl_3$) δ 8.11 (d, J=9.2 Hz, 1H), 7.37-7.24 (m, 5H), 7.21 (d, J=2.7 Hz, 1H), 6.94 (dd, J=9.2 and 2.7 Hz, 1H), 5.26 (d, J=5.2 Hz, 1H), 3.93 (s, 3H), 3.41-3.30 (m, 1H), 1.46 (d, J=7.1 Hz, 3H); ^{13}C nmr ($CDCl_3$) δ 163.5, 141.2, 140.5, 133.0, 128.8, 128.7, 127.6, 127.3, 118.8, 116.5, 113.8, 56.1, 43.0, 42.4, 16.0; ms (m/z, relative intensity) 296 (M^+, 5), 192 (5), 176 (5), 105 (100); $[\alpha]^{25}$ = -115° (c=1, $CHCl_3$). Anal. Calcd for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.44; N, 9.45. Found: C, 68.51; H, 5.43; N, 9.33.

2-(R,S)-(5-Methoxy-2-nitrophenyl)-3-(S)-methyl-3-phenylpropionitrile (2e).
2-(2-Nitro-5-methoxyphenyl)acetonitrile and R-(+)-*sec*- phenethyl alcohol were used, and chromatography using 1:3 ethyl acetate/hexanes afforded **2e** (56%) as a 2:3 mixture of diastereomers (less polar:most polar). The first diastereomer eluted was a yellow solid (mp, 109.5-111.5 °C) whose spectral and physical properties were identical to the less polar diastereomer of **2d**, except: $[\alpha]^{25} = -13°$ (c=1, $CHCl_3$). Further elution afforded the second (more polar) diastereomer as a yellow oil whose spectral and physical properties were identical to the more polar diastereomer of **2d**, except: $[\alpha]^{25} = +117°$ (c=1, $CHCl_3$).

2-(5-Methoxy-2-nitrophenyl)propionitrile (2f).
2-(2-Nitro-5-methoxyphenyl)acetonitrile and methanol were used, and chromatography using 2:3 ether/hexanes afforded **2f** (45%) as a yellow solid: mp, 61.5-63.0 °C; ir ($CHCl_3$) 2240, 1607, 1584, 1341, 1296 cm^{-1}; ^1H nmr ($CDCl_3$) δ 8.12 (d, J=9.2 Hz, 1H), 7.21 (d, J=2.7 Hz, 1H), 6.93 (dd, J=9.2 and 2.7 Hz, 1H), 4.90 (q, J=7.0 Hz, 1H), 3.92 (s, 3H), 1.68 (d, J=7.0 Hz, 3H); ^{13}C nmr ($CDCl_3$) δ 164.0, 140.1, 135.5, 128.7, 120.8, 114.8, 113.8, 56.1, 28.6, 21.1; ms (m/z, relative intensity) 206 (M^+, 71), 189 (100), 172 (33), 157 (31), 146 (23), 134 (37). Anal. Calcd for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.89; N, 13.59. Found: C, 58.19; H, 4.89; N, 13.51.

2-(6-Methoxy-3-nitropyrid-2-yl)propionitrile (2g).
2-(3-Nitro-6-methoxypyrid-2-yl)acetonitrile and methanol were used, and chromatography using 2:3 ether/hexanes afforded **2g** (66%) as a yellow solid: mp 59.5-62.5 °C; ir ($CHCl_3$) 2245, 1591, 1473, 1334, 1291 cm^{-1}; ^1H nmr ($CDCl_3$) δ 8.35 (d, J=9.1 Hz, 1H), 6.84 (d, J=9.0 Hz, 1H), 5.02 (q, J=7.0 Hz, 1H), 4.13 (s, 3H), 1.77 (d, J=7.0 Hz, 3H); ^{13}C nmr ($CDCl_3$) δ 165.6, 151.0, 138.0, 136.7, 119.6, 111.7, 55.2, 32.0, 18.9; ms (m/z, relative intensity) 207 (M^+, 75), 190 (100), 180 (38), 159 (39), 148 (25), 134 (51), 118 (43), 104 (33). Anal. Calcd for $C_9H_9N_3O_3$: C, 52.17; H, 4.38; N, 20.28. Found: C, 52.49; H, 4.44; N, 20.32.

2-(5-Methoxy-2-nitrophenyl)pent-4-enenitrile (2h).
2-(2-Nitro-5-methoxyphenyl)acetonitrile and allyl alcohol were used, and chromatography using 2:3 ether/hexanes afforded **2h** (70%) as a pale orange oil: Ir ($CHCl_3$) 2239, 1605, 1582, 1341, 1295 cm^{-1}; ^1H nmr ($CDCl_3$) δ 8.18 (d, J=9.2 Hz, 1H), 7.21 (d, J=2.7 Hz, 1H), 6.96 (dd, J=9.2 and 2.7 Hz, 1H), 5.97-5.83 (m, 1H), 5.27-5.19 (m, 2H), 4.99 (dd, J=8.6 and 5.0 Hz, 1H), 3.95 (s, 3H), 2.81-2.69 (m, 1H), 2.65-2.54 (m, 1H); ^{13}C nmr ($CDCl_3$) δ 163.8, 140.2, 133.5, 131.9, 128.7, 120.2, 119.6, 115.6, 113.9, 56.2, 39.1, 34.5; ms (m/z, relative intensity) 233 (MH^+, 4), 215 (8), 191 (35), 186 (87), 160 (99), 159 (100), 144 (53), 109 (96). Anal. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.07; H, 5.21; N, 12.06. Found: C, 62.01; H, 5.39; N, 11.93.

2-(5-Methoxy-2-nitrophenyl)pent-4-ynenitrile (2i).
2-(2-Nitro-5-methoxyphenyl)acetonitrile and propargyl alcohol were used, and chromatography using 2:3 ether/hexanes afforded **2i** (56%) as a pale yellow solid: mp 58.0-59.5 °C; ir ($CHCl_3$) 3304, 2242, 1605, 1583, 1340 cm^{-1}; ^1H nmr ($CDCl_3$) δ 8.19 (d, J=9.2 Hz, 1H), 7.32 (d, J=2.7 Hz, 1H), 6.99 (dd, J=9.2 and 2.7 Hz, 1H), 5.15 (dd, J=6.4 and 5.4 Hz, 1H), 3.96 (s, 3H), 3.06-2.80 (m, 2H), 2.20 (t, J=2.7 Hz, 1H);

^{13}C nmr ($CDCl_3$) δ 163.8, 140.1, 132.0, 128.7, 118.8, 116.2, 114.4, 77.8, 73.2, 56.2, 33.6, 24.8; FABms (m/z, relative intensity) 230 (M^+, 3), 184 (100), 169 (21), 140 (24), 106 (20). Anal. Calcd for $C_{12}H_{10}N_2O_3$: C, 62.61; H, 4.38; N, 12.17. Found: C, 62.74; H, 4.42; N, 11.93.

2-(6-Methoxy-3-nitropyrid-2-yl)pent-4-ynenitrile (2j).

2-(3-Nitro-6-methoxypyrid-2-yl)acetonitrile and propargyl alcohol were used, and chromatography using 1:3 ethyl acetate/hexanes afforded **2j** (76%) as a pale yellow oil: ir ($CHCl_3$) 3304, 2244, 1588, 1473, 1336, 1295 cm^{-1}; ^1H nmr ($CDCl_3$) δ 8.37 (d, J=9.1 Hz, 1H), 6.88 (d, J=9.0 Hz, 1H), 5.22 (t, J=7.2 Hz, 1H), 4.12 (s, 3H), 3.04 (dd, J=7.2 and 2.6 Hz, 2H), 2.13 (t, J=2.6 Hz, 1H); ^{13}C nmr ($CDCl_3$) δ 165.5, 147.9, 138.8, 136.7, 117.5, 112.2, 78.1, 72.4, 55.3, 36.4, 22.9; ms (m/z, relative intensity) 231 (M^+, 18), 230 (53), 214 (66), 184 (100), 155 (40), 142 (48), 118 (52), 103 (40). Anal. Calcd for $C_{11}H_9N_3O_3$: C, 57.14; H, 3.92; N, 18.23. Found: C, 56.74; H, 4.18; N, 18.23.

2-(5-Methoxy-2-nitrophenyl)pentanenitrile (2k).

2-(2-Nitro-5-methoxyphenyl)acetonitrile and propyl alcohol were used, and chromatography using 2:3 ether/hexanes afforded **2k** (72%) as a pale orange solid: mp 60.0-62.0 °C; ir (KBr) 2240, 1615, 1580, 1515, 1485, 1465 cm^{-1}; ^1H nmr ($CDCl_3$) δ 8.13 (d, J=9.2 Hz, 1H), 7.19 (d, J=2.7 Hz, 1H), 6.93 (dd, J=9.2 and 2.7 Hz, 1H), 4.88 (dd, J=9.0 and 5.1 Hz, 1H), 3.92 (s, 3H), 1.92-1.75 (m, 2H), 1.72-1.56 (m, 2H), 0.98 (t, J=7.3 Hz, 3H); ^{13}C nmr ($CDCl_3$) δ 163.9, 140.1, 134.6, 128.6, 120.1, 115.2, 113.7, 56.1, 37.4, 34.1, 20.7, 13.2; ms (m/z, relative intensity) 234 (M^+, 44), 217 (92), 175 (100), 146 (55), 120 (43), 106 (71). HRms calcd for $C_{12}H_{14}N_2O_3$ 234.1024, found 234.0984. Anal. Calcd for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.23; H, 6.03; N, 11.79.

N-(2-(6-methoxy-3-nitropyrid-2-yl)-3-cyanopropyl)phthalimide (2m).

2-(3-Nitro-6-methoxypyrid-2-yl)acetonitrile and N-(2-hydroxyethyl)phthalimide were used, and chromatography using 1:1 ether/hexanes afforded **2m** (5%) as a pale yellow solid: mp 128.0-133.0 °C; ir (KBr) 3100, 2260, 1770, 1715, 1600, 1585, 1525, 1480 cm^{-1}; ^1H nmr ($CDCl_3$) δ 8.32 (d, J=9.1 Hz, 1H), 7.88-7.83 (m, 2H), 7.77-7.73 (m, 2H), 6.79 (d, J=9.1 Hz, 1H), 5.01 (dd, J=8.1 and 5.9 Hz, 1H), 4.12 (s, 3H), 4.01-3.93 (m, 2H), 2.60-2.47 (m, 2H); ms (m/z, relative intensity) 349 (8), 332 (5), 206 (33), 193 (52), 160 (100). Anal. Calcd for $C_{18}H_{14}N_4O_5$: C, 59.02; H, 3.85; N, 15.29. Found: C, 58.86; H, 3.83; N, 15.02.

2-Cyclohexyl-2-(2-nitro-5-methoxyphenyl)acetonitrile (2n).

2-(2-Nitro-5-methoxyphenyl)acetonitrile and cyclohexanol were used, and chromatography using 90:9:1 petroleum ether/methylene chloride/acetone afforded **2n** (27%) as a pale brown oil: ir ($CHCl_3$) 2240, 1603, 1583, 1347, 1296 cm^{-1}; ^1H nmr ($CDCl_3$) δ 8.18 (d, J=9.2 Hz, 1H), 7.16 (d, J=2.7 Hz, 1H), 6.95 (dd, J=9.2 and 2.7 Hz, 1H), 4.95 (d, J=4.7 Hz, 1H), 3.94 (s, 3H), 1.85-1.66 (m, 6H), 1.34-1.14 (m, 5H); ^{13}C nmr ($CDCl_3$) δ 163.4, 140.6, 133.1, 128.7, 119.2, 116.1, 113.6, 56.1, 42.0, 40.6, 31.6, 29.7, 28.6, 26.0, 25.7; ms (m/z, relative intensity) 274 (M^+, 8), 257 (3), 192 (56), 175 (100), 121 (31), 106 (27). Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.79; H, 6.76; N, 9.98.

2-Cyclohexyl-2-(6-methoxy-3-nitropyrid-2-yl)acetonitrile (2o).

2-(3-Nitro-6-methoxypyrid-2-yl)acetonitrile and cyclohexanol were used, and chromatography using 1:4 ether/hexanes afforded **2o** (35%) as a yellow solid: mp 51.0-53.0 °C; ir ($CHCl_3$) 2240, 1590, 1471, 1335, 1307, 1288 cm^{-1}; ^1H nmr ($CDCl_3$) δ 8.35 (d, J=9.1 Hz, 1H), 6.82 (d, J=9.1 Hz, 1H), 4.95 (d, J=6.0 Hz, 1H), 4.11 (s, 3H), 2.12-1.97 (m, 1H), 1.88-1.60 (m, 5H), 1.40-1.16 (m, 5H); ^{13}C nmr ($CDCl_3$) δ 165.0, 149.8, 138.8, 136.7, 118.1, 111.4, 55.2, 43.6, 41.5, 31.4, 29.5, 26.0, 25.8, 25.7; ms (m/z, relative intensity) 276 (MH^+, 6), 258 (6), 207 (6), 176 (100), 166 (34), 148 (14), 134 (9). Anal. Calcd for $C_{14}H_{17}N_3O_5$: C, 61.08; H, 6.22; N, 15.26. Found: C, 61.03; H, 6.23; N, 15.19.

General Synthesis of 3-Alkylindoles and 3-Alkylpyrrolo[3,2-b]pyridines (3).

A mixture of a 2-alkyl-2-(2-nitro-5-methoxyaryl)acetonitrile (**2**, 2.00 mmol) and 10% Pd on carbon (100 mg) in ^{n}butanol (15 ml) was shaken under a hydrogen atmosphere (3 atm) at 80 °C overnight (12-24 h). The resulting reaction mixture was filtered through Celite® and evaporated under reduced pressure. The residue was chromatographed using silica gel (approx 50 g) using an appropriate solvent system to afford the corresponding indole or pyrrolo[3,2-b]pyridine(3).

3-Benzyl-5-methoxyindole (3a).

2-(5-Methoxy-2-nitrophenyl)-3-phenylpropionitrile (**2a**) was used. Chromatography using 30% ethyl acetate in hexanes afforded **3a** (54%) as an off-white solid: mp 59.0-62.0 °C; ir (KBr) 3315, 1620, 1580, 1485, 1445, 1435 cm^{-1}; ^1H nmr ($CDCl_3$) δ 7.89 (br s, NH), 7.36-7.24 (m, 5H), 7.26 (d, J=8.8 Hz, 1H), 7.02 (d, J=2.3 Hz, 1H), 6.91 (dd, J=8.8 and 2.4 Hz, 1H), 6.89 (d, J=2.0 Hz, 1H), 4.14 (s, 2H), 3.86 (s, 3H); ^{13}C nmr ($CDCl_3$) δ 153.9, 141.2, 131.6, 128.7, 128.3, 127.9, 125.9, 123.2, 115.5, 112.2, 111.8, 101.1, 55.9, 31.6; ms (m/z, relative intensity) 237 (M^+, 100), 222 (8), 160 (61). Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.83; H, 6.31; N, 5.81.

5-Methoxy-3-(4-methoxyphenylmethyl)indole (3b).

2-(5-Methoxy-2-nitrophenyl)-3-(4-methoxyphenyl)propionitrile (**2b**) was used. Chromatogra-phy using 10% ethyl acetate in hexanes afforded **3b** (50%) as a pale yellow solid: mp 93.0-95.0 °C; ir (KBr) 3410, 3395, 1625, 1615, 1515, 1490, 1440 cm^{-1}; ^1H nmr ($CDCl_3$) δ 7.85 (br s, NH), 7.25 (d, J=8.4 Hz, 2H), 7.22 (d, J=8.8 Hz, 1H), 6.96 (d, J=2.3 Hz, 1H), 6.90-6.82 (m, 4H), 4.04 (s, 2H), 3.83 (s, 3H), 3.80 (s, 3H); ^{13}C nmr ($CDCl_3$) δ 157.8, 153.9, 133.2, 131.6, 129.6, 127.9, 123.1, 116.0, 113.8, 112.1, 111.7, 101.1, 55.9, 55.3, 30.7; ms (m/z, relative intensity) 267 (M^+, 41), 252 (4), 160 (88), 83 (100); HRms calcd for $C_{17}H_{17}NO_2$ 267. 1273, found 267.1257. Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.39; H, 6.41; N, 5.24. Found: C, 75.99; H, 6.54; N, 5.10.

(R)-5-Methoxy-3-(1-phenylethyl)indole (3d).

2-(R,S)-(5-Methoxy-2-nitrophenyl)-3-(R)-methyl-3-phenylpropionitrile (**2d**) was used. Chromatography using 1:4 ethyl acetate/hexanes afforded **3d** (58%) as a pale yellow solid: mp 134.0-135.0 °C; ir (KBr) 3360, 1630, 1620, 1605, 1590, 1580, 1490, 1455, 1445 cm^{-1}; ^1H nmr ($CDCl_3$) δ 7.86 (br s, NH), 7.33-7.15 (m, 6H), 7.01 (br s), 6.82 (dd, J=8.6 and 2.5 Hz, 1H), 6.79 (d, J=2.2 Hz, 1H),

4.34 (q, J=7.1 Hz, 1H), 3.74 (s, 3H), 1.71 (d, J=7.1 Hz, 3H); ^{13}C nmr ($CDCl_3$) δ 153.7, 146.7, 131.8, 128.3, 127.4, 127.3, 125.9, 121.9, 121.2, 111.9, 111.6, 101.8, 55.8, 37.0, 22.3; ms (m/z, relative intensity) 251 (M^+, 91), 236 (100), 220 (24), 204 (33), 192 (24), 174 (31), 165 (25), 101 (33); $[\alpha]^{25}$ = +59° (c=1, $CHCl_3$). Anal. Calcd for $C_{17}H_{17}NO$: C, 81.25; H, 6.82; N, 5.57. Found: C, 81.17; H, 6.87; N, 5.55.

(S)-5-Methoxy-3-(1-phenylethyl)indole (3e).

2-(R,S)-(5-Methoxy-2-nitrophenyl)-3-(S)-methyl-3-phenylpropionitrile (**2e**) was used. Chromatography using 1:4 ethyl acetate/hexanes afforded **3e** (42%) as a pale yellow solid (mp 128.0-132.0 °C) whose spectral and physical properties were identical to **3d**, except: $[\alpha]^{25}$ = -54° (c=1, $CHCl_3$). Anal. Calcd for $C_{17}H_{17}NO$: C, 81.25; H, 6.82; N, 5.57. Found: C, 80.90; H, 6.94; N, 5.37.

3-Methylpyrrolo[3,2-b]pyridine (3g).

2-(6-Methoxy-3-nitropyrid-2-yl)propionitrile (**2g**) was used. Chromatography using 1:4 ether/hexanes afforded **3g** (16%) as a pale brown oil: ^1H Nmr ($CDCl_3$) δ 7.96 (br s, NH), 7.52 (d, J=8.7 Hz, 1H), 7.11 (d, J=1.3 Hz, 1H), 6.60 (d, J=8.7 Hz, 1H), 4.03 (s, 3H), 2.36 (s, 3H); ms (m/z, relative intensity) 162 (M^+, 28), 146 (14), 133 (15), 100 (28), 91 (34), 83 (100); HRms calcd for $C_9H_{10}N_2O$ 162.0810, found 162.0802.

5-Methoxy-3-propylindole (3k).

2-(5-Methoxy-2-nitrophenyl)pent-4-ynenitrile (**2l**) was used. Chromatography using 10% ethyl acetate in hexanes afforded **3k** (41%) as a pale yellow oil: Ir ($CHCl_3$) 3478, 1621, 1584, 1477, 1451 cm^{-1}; ^1H nmr ($CDCl_3$) δ 7.83 (br s, NH), 7.26 (d, J=8.8Hz, 1H), 7.11 (d, J=2.4 Hz, 1H), 6.97 (br s, 1H), 6.91 (dd, J=8.8 and 2.4 Hz, 1H), 3.93 (s, 3H), 2.76 (t, J=7.5 Hz, 2H), 1.84-1.69 (m, 2H), 1.07 (t, J=7.3 Hz, 3H); ^{13}C nmr ($CDCl_3$) δ 153.8, 131.6, 128.0, 122.1, 116.7, 111.9, 111.8, 101.0, 56.0, 27.3, 23.2, 14.2; ms (m/z, relative intensity) 189 (M^+, 35), 160 (100), 145 (10), 117 (10), 69 (33); HRms calcd for $C_{12}H_{15}NO$ 189.1167, found 189.1161.

5-Methoxy-3-propylindole (3k).

2-(5-Methoxy-2-nitrophenyl)pentanenitrile (**2k**) was used. Chromatography using 10% ethyl acetate in hexanes afforded **3k** (42%) as a pale yellow oil identical in its spectral and physical properties with the material described above.

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REFERENCES

1. O. Mitsunobu, *Synthesis*, 1981, 1.

2. M. Varasi, K. A. M. Walker, and M. L. Maddox, *J. Org. Chem.*, 1987, **52**, 4235.

3. Part of this work has been presented in preliminary form: J. E. Macor and J. M. Wehner, *Tetrahedron Lett.*, 1991, **32**, 7195.

4. M. Makosza, W. Danikiewicz, and K. Wojciechowski, *Liebigs Ann. Chem.*, 1988, 203.

5. T. H. Lowry, and K. S. Richarson, 'Mechanism and Theory in Organic Chemistry', Harper and Row Publishers, New York, 1981, pp. 342-349.

6. Other researchers have come to this same conclusions albeit via different interpretations of the reaction mechanism: see: a) reference 2; and b) D. L. Hughes, R. A. Reamer, J. J. Bergan, and E. J. J. Grabowski, *J. Am. Chem. Soc.*, *1988*, **110**, 6487.

7. A. Pautrad-Cooper and S. A. Evans Jr., *J. Org. Chem.*, 1989, **54**, 2485.

8. a) E. Grochowski, B. D. Hilton, R. J. Kupper, and C. J. Michejda, *J. Am. Chem. Soc.*, 1982, **104**, 6876; b) M. Von Itzstein and I. D. Jenkins, *Aust. J. Chem.*, 1983, **36**, 557.

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