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Synthesis of 2-aryl-2*H*-indazoles by base catalysed reaction of 2-nitrobenzyl triphenylphosphonium bromide and aryl isocyanates

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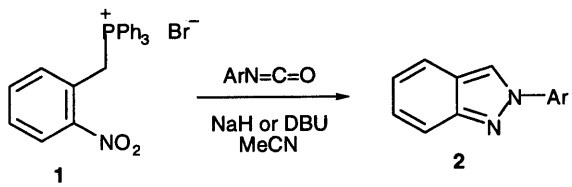
Abstract

The synthesis of a series of 2-aryl-2*H*-indazoles is reported. These compounds are obtained in moderate to good yield by reaction of 2-nitrobenzyl triphenylphosphonium bromide with aryl isocyanates, catalysed by sodium hydride or DBU.

As part of our studies on developing new heterocyclisation reactions,[1] we have been investigating reactions where the nitrogen atom of a nitro substituent on an aromatic or heteroaromatic ring undergoes transformation into a new heterocyclic ring nitrogen. We have shown that nitroimidazolyl phosphoramidates undergo reaction with aryl isocyanates to form imidazo fused [1,2,3]triazoles,[2] and now wish to report our findings on the reaction of nitrobenzyl phosphonium salts with aryl isocyanates (Scheme 1). We have found that 2-nitrobenzyl triphenylphosphonium bromide reacts smoothly with aryl isocyanates in the presence of a base, such as sodium hydride or DBU, to form 2-aryl-2*H*-indazoles in moderate to good yield; the nitro group nitrogen being transformed into the indazole N-1 atom.



Scheme 1.

Indazoles are pharmacologically important compounds and the indazole ring system forms the basis of a number of drug molecules including granisetron,[3] a 5-HT_3 receptor antagonist

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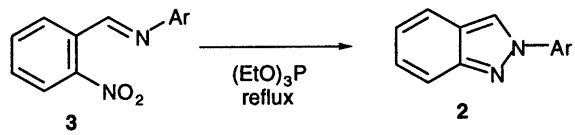
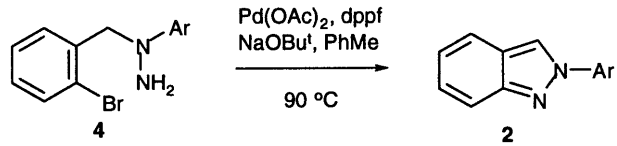
used as an anti-emetic in cancer chemotherapy, and benzydamine,[4] an anti-inflammatory agent. Indazoles[5] can be synthesised by a number of methods, usually involving formation of the N–N bond as the key step. One of the now classical methods[6] for their synthesis is the deoxygenation of 2-nitroanils **3** with triethyl phosphite, developed by Cadogan and Mackie, shown in Scheme 2.



3 2

Scheme 2.

More recently Song and Yee[7] have used a palladium catalysed cyclisation of bromobenzyl aryl hydrazines **4** (Scheme 3) to synthesise indazoles, in this case forming a C–N bond as the key ring closing step. Our route to indazoles also employs a nitro compound with readily available nitrobenzyl triphenylphosphonium bromide acting as the starting material. Deprotonation to form the purple ylide can be easily be effected with a range of bases. We have found DBU to be the best base to use in this reaction. Treatment of the ylide with an aryl isocyanate and heating the mixture at 60°C in acetonitrile then affords the 2-aryl indazoles† shown in Table 1.



4 2

Scheme 3.

Table 1
Indazoles **2** synthesised†

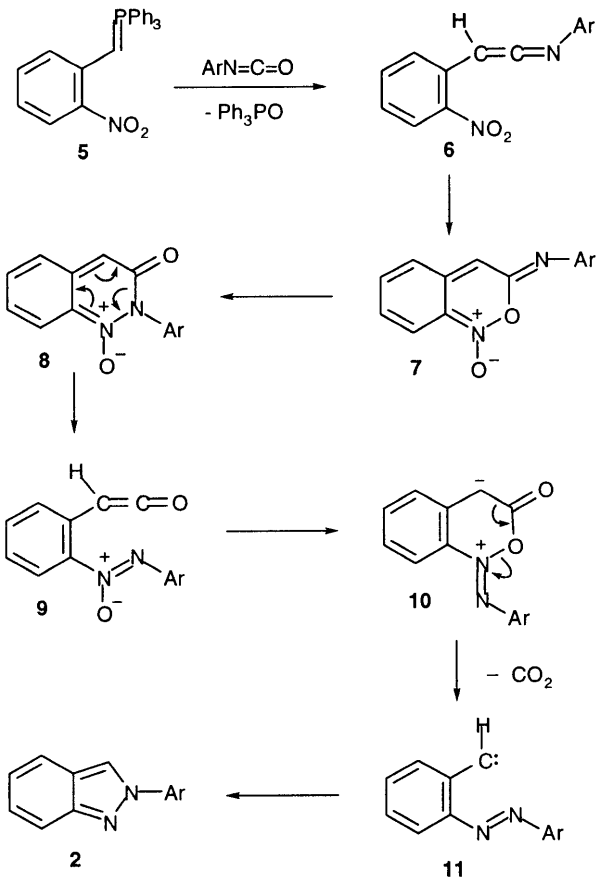
	Ar	Yield (%)
a	4-$MeOC_6H_4$	57[6,10]
b	4-$PhOC_6H_4$	45
c	2-MeO-3-MeC_6H_3	40
d	4-EtO_2C–C_6H_4	60[11,12]
e	4-F–C_6H_4	55[11,13]
f	3,4,5-$(MeO)_3C_6H_2$	62
g	3-NC–C_6H_4	53[11]

The reaction works for aryl isocyanates with either electron withdrawing, or electron donating substituents. Sodium hydride can also be employed as the base, although in this case the indazoles were accompanied by small amounts of 2-nitrotoluene as a by-product. We believe this is formed by traces of sodium hydroxide in the hydride reagent which attack the phosphonium

† New compounds exhibited satisfactory analytical and spectroscopic data.

cation forming a pentacoordinate phosphorane. This can then cleave to form triphenylphosphine oxide, and the nitrotoluene anion, which is subsequently protonated during work-up.

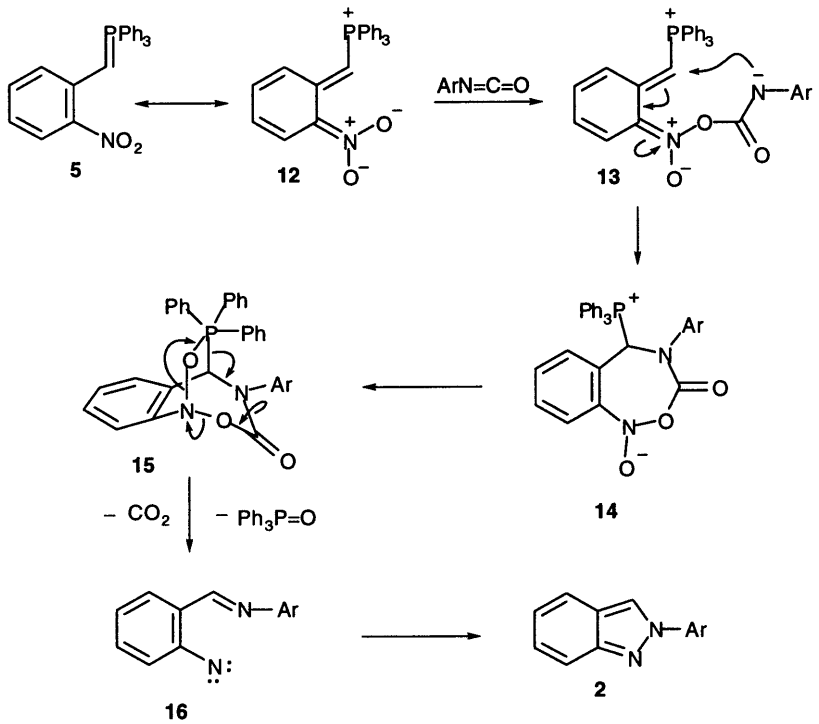
The reaction to form the indazole ring involves loss of triphenylphosphine oxide and carbon dioxide, and several mechanisms can be considered to transform the nitro compound into the indazole nucleus. We have considered two possible pathways as the most likely that could lead to closure of the pyrazole ring. In the first case a Wittig reaction may occur between the ylide **5** and the isocyanate to form a ketimine such as **6** (Scheme 4). This could undergo attack by an oxygen atom of the adjacent nitro group leading to **7**. Ring opening and reclosure through the aryl-substituted nitrogen would generate the cinnoline-*N*-oxide **8**. A second ring opening would produce the ketene **9**, which may be attacked by the oxygen atom of the neighbouring azoxy group to form **10**. Loss of carbon dioxide would then produce the azo-carbene intermediate **11**, which would readily undergo electrocyclic ring closure to form the 2-indazole. Such a mechanism is closely related to that proposed by Rees[8] to account for the formation of phenyl benzotriazole in the thermolysis of 2-nitrophenyl carbodiimide.



Scheme 4.

Alternatively a mechanism involving acylation of a nitro group oxygen atom may operate to form an acyl nitronate intermediate of the type **13** (Scheme 5). Aliphatic nitro compounds are known to undergo acylation by isocyanates in the dehydration reaction, to form nitrile oxides.[9]

We can find no reports on the acylation of aromatic nitro compounds, and aryl isocyanates are inert to nitrobenzene and 2-nitrotoluene up to 150°C. It is possible that the aryl nitro substituent is more nucleophilic, due to delocalisation of negative charge from the ylide carbon, as shown by resonance structure **12**. Delocalisation is supported by the intense purple colour of the ylide. The acyl nitronate could then be converted into the indazole as shown in Scheme 5. Cyclisation of the carbamate nitrogen onto the methine carbon would produce the seven-membered ring intermediate **14**. Triphenylphosphine oxide and carbon dioxide could then be lost from the bridged structure **15** to generate the indazole ring. Loss of these two compounds may equally well be separate events. At present we have no evidence to support either of the two pathways and further work is underway to determine the mechanism of this reaction which will be reported in due course.



Scheme 5.

In summary we believe this reaction represents a convenient way to synthesise indazole derivatives substituted at the 2-position with a variety of aromatic groups.

Acknowledgements

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