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Access to *1H*-indazoles, *1H*-benzoindazoles and *1H*-azaindazoles from (het)aryl azides: a Staudinger-aza-Wittig tandem reaction leading to N-N bond formation?

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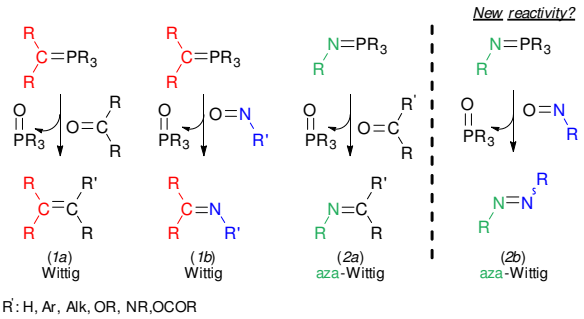
The synthesis of various substituted 1H-indazoles is reported through N-N bond formation from an iminophosphorane derivative. Supported by control experiments, an original Staudinger-aza-Wittig tandem mechanism is proposed for this transformation.

The Wittig reaction,[1] first disclosed in the early 1950s, is a reliable way to synthetize regio- and stereo-selective olefins from easily accessible starting materials in mild reaction conditions (Scheme 1, eq. 1a). It remains a well-known and widely used approach and is still the subject of recent development.[2] Replacement of the phosphorane group in the Wittig olefination reaction by an iminophosphorane group leads to an aza-Wittig reaction with formation of an imine bond (Scheme 1, eq. 2a). This powerful way to create a C=N bond depends on the combination of the nucleophilicity of the iminophosphorane involved and the subsequent elimination of oxidized phosphorus. Various electrophiles such as aldehyde, ketone, ester and amide have indeed been successfully used in inter- and intramolecular manners.[3]



Scheme 1: State of the art and project plan

We herein disclose the use of an electrophilic nitrogen as a possible partner to form an N-N double bond through an aza-Wittig reaction (Scheme 1, eq. 2b). Our interest focused on the nitroso group, whose isoelectronic similarity with the carbonyl group is established. Its behavior in the Wittig reaction has scarcely been studied despite its prompt conversion into imine (Scheme 1, eq. 1b).[4] This lack of attention is probably due to the rather difficult access to the *C*-nitroso moiety compared to iminophosphorane,[5] whereas the resulting imine product is similar. *C*-nitroso compounds can indeed be oxidized or isomerized, nevertheless a large variety of reliable synthetic routes are available to address these issues.[6] A previous attempt to perform an aza-Wittig reaction, using a *C*-nitroso derivative as the electrophile, was made by Staudinger and Hauser in 1921 but the triphenyl iminophosphorane failed to react with nitrosobenzene.[7] Later, the use of the more nucleophilic arsenic ylide enabled this absence of reactivity to be overcome and was applied to the synthesis of electron deficient azobenzenes.[8] To the best of our knowledge, only one study postulates an intramolecular aza-Wittig mechanism involving an iminophosphorane and a *N*-nitroso compound.[9]

In our approach, the N=N bond formation would result from an intramolecular aza-Wittig reaction with a C-nitroso group coming from the *in situ* nitrosation on the activated methylene. This intramolecular sequential domino reaction would provide, after isomerization, a *1H*-indazole scaffold (Scheme 2). Apart from an original access to useful heterocyclic derivatives[10] and more particularly to 1H-indazoles,[11] the aim of this study is to underline an unusual reactivity of azides as alternative starting materials.

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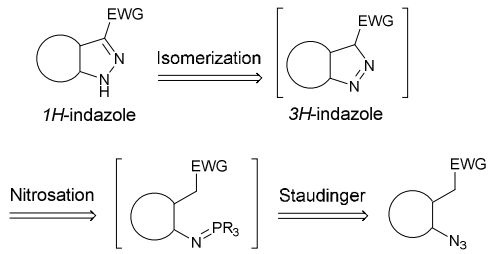
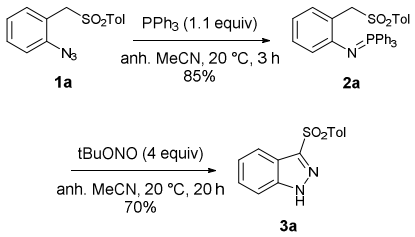


Scheme 2: Envisaged retrosynthesis

This reaction was first observed with the iminophosphorane **2a**, synthetized from **1a** in the presence of an excess of triphenylphosphine in anhydrous acetonitrile (Scheme 3). In the presence of *tert*-butyl nitrite in anhydrous acetonitrile, **2a** gave rise to the formation of the desired *1H*-indazole **3a** in 70% yield without any additives or catalysts, validating our synthetic approach.



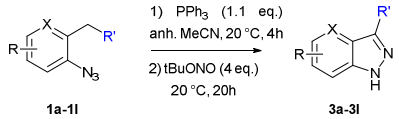
Scheme 3: Sequential formation of **3a**

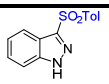
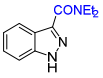
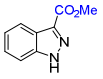
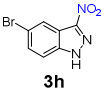
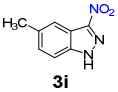
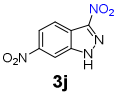
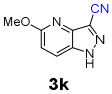
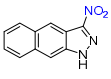
Then, a sequential domino process was tried (Table 1). In this way, **3a** was isolated with excellent 69% yield. Next, several electron withdrawing groups were examined as activating agents of the methylene position. In addition to sulfonyl substituents, our synthetic process tolerates nitrile, nitro, amide and ester groups and enables the clean formation of the expected products with good to excellent yields. Surprisingly, when 2-(2-azidophenyl)acetic acid **1f** was used, a spontaneous decarboxylation occurred leading to the unsubstituted *1H*-indazole **3f** in 51% yield. The requirement of an activated methylene for the nitrosation step was verified with 1-azido-2-(methoxymethyl)benzene **3g**. In the presence of an electron donating group, the sequential domino process did not occur, only the iminophosphorane was recovered. Increasing the temperature or adding a base for the nitrosation step did not bring about any improvement.

However, it is worth noting that substituents on the phenyl ring such as bromide, alkyl or nitro groups were well-tolerated since **3h-j** were successfully isolated in good to excellent yields. The procedure was also applied to pyridyl (**3k**) and naphthyl (**3l**) scaffolds.

To get some insight into the reaction mechanism, some control experiments were performed (Scheme 4). Apart from being a nitrosating agent, *tert*-butyl nitrite is also described to react with amines to give diazonium intermediates.[12] In order to exclude such a diazotation pathway from an iminophosphorane, the triphenyliminophosphorane **5** was reacted with *tert*-butyl nitrite (Scheme 4, a) and $NaNO_2$ in AcOH.[9] After 20 h at room temperature, the starting material **5** was fully recovered with only traces of the reduced amine **6**, allowing us to assume that a diazotization process cannot be considered here.

Table 1. Sequential domino sequence[‡]



Entry	1	X	R	R'	3	Yield (%)
1	**1a**	CH	H	SO_2Tol	 **3a**	69
2	**1b**	CH	H	CN	 **3b**	92
3	**1c**	CH	H	NO_2	 **3c**	87
4	**1d**	CH	H	$CONEt_2$	 **3d**	71
5	**1e**	CH	H	CO_2Me	 **3e**	77
6	**1f**	CH	H	CO_2H	 **3f**	51[a]
7	**1g**	CH	H	OMe	 **3g**	-[b]
8	**1h**	CH	Br	NO_2	 **3h**	87
9	**1i**	CH	CH_3	NO_2	 **3i**	84
10	**1j**	CH	NO_2	NO_2	 **3j**	57
11	**1k**	N	OMe	CN	 **3k**	80
12	**1l**	CH	Ph	NO_2	 **3l**	40

[a] 2-(2-Azidophenyl)acetic acid **1f** was used as starting material and an *in situ* decarboxylation was observed. [b] Degradation.

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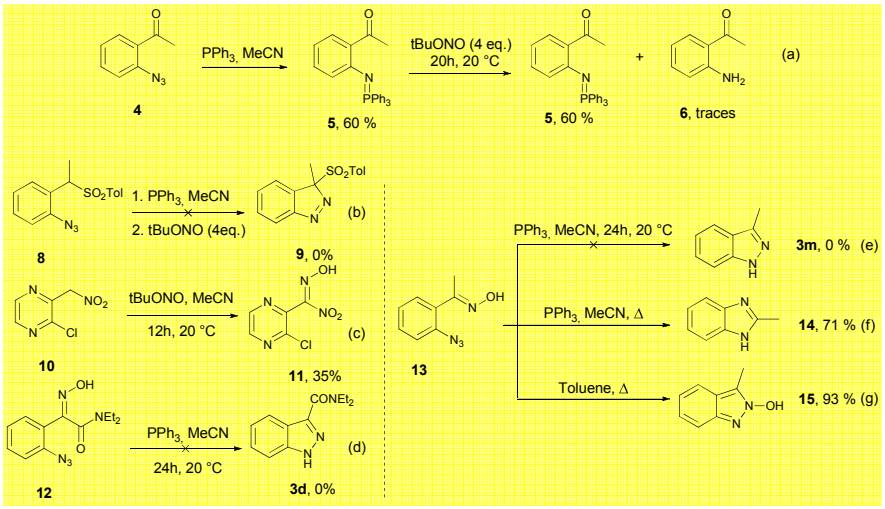
We then focused our attention on the nitrosation step. In order to isolate and characterize the assumed nitroso intermediate, and avoid—tautomeric equilibrium to the corresponding oxime,



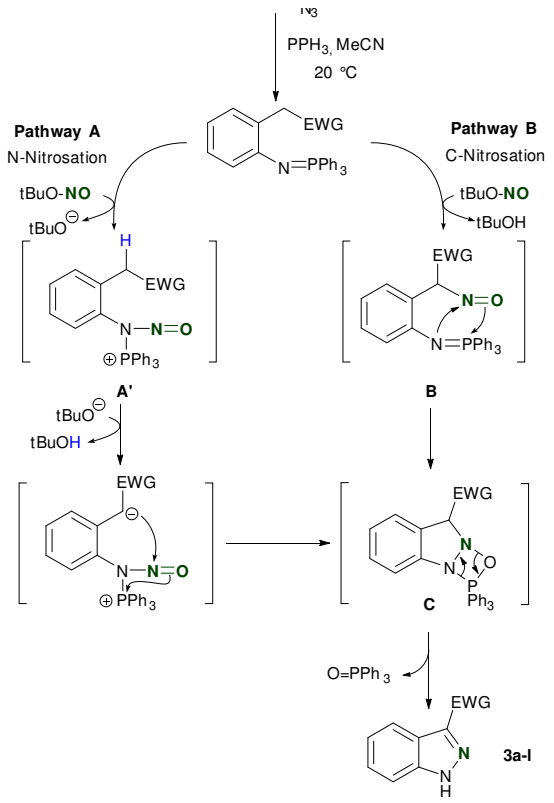
Scheme 4: Control experiments

the azide **8** bearing a tertiary carbon at the activated benzylic position was used as substrate. Unfortunately, only degradation was observed when *tert*-butyl nitrite was introduced into the reaction mixture (Scheme 4, b).

However, we evidenced a *C*-nitrosation reaction using compound **10**, which possesses an activated methylene, by recovering the tautomeric oxime **11** (Scheme 4, c).

At this stage, we wondered if the nitroso function could come from such tautomeric equilibrium. To answer this question, the oxime **12** was subjected to the standard conditions i.e. in acetonitrile at room temperature (Scheme 4, d). After 24 h, the reaction mixture was degraded. The same result was observed with **13** (Scheme 4, e). The absence of the expected *1H*-indazoles **3d** and **3m** confirms that the oxime moiety, through the nitroso form or not, does not react with the iminophosphorane intermediate under these reaction conditions. It is worth noting that in refluxing toluene, a nitrene type cyclization occurred in the absence of triphenylphosphine (Scheme 4, g)[13] while in the presence of triphenylphosphine, a Beckmann type rearrangement (*de facto* phosphine assisted) efficiently led to the 2-methyl-*1H*-benzimidazole **11** (scheme 4, f). In both cases, no trace of the expected product **3m** was observed.

Based on literature reports[14] and our observations, a plausible mechanism has been proposed (Scheme 5). First, the introduction of triphenylphosphine to the medium enables the straightforward formation of an iminophosphorane moiety through a Staudinger reaction. Then two intermediates may result through an N- or C-nitrosation thanks to the presence of either the nucleophilic nitrogen (intermediate A) or the activated methylene (intermediate **B**). Then, a cyclisation can occur leading to an oxadiazaphosphetidine **C**. Noteworthy from pathway **A**, the activated methylene would be deprotonated by the *ter*-butylate side product from the nitrosation reaction and from pathway **B**, the *in situ* cycloaddition of the iminophosphorane onto the nitroso N=O double bond should be faster than the isomerization of the latter into an oxime moiety. Then, according to the accepted Wittig mechanism, a [2+2] cycloreversion reaction would follow with the formation of triphenylphosphine oxide and *3H*-indazole, which would directly tautomerize to the stable *1H*-indazole **3**.



Scheme 5:-Plausible mechanism

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Conclusions

We report herein the unprecedented reaction between an iminophosphorane and a nitroso moiety through a probable Staudinger / aza-Wittig tandem reaction. This novel approach was investigated from a mechanistic point of view and applied to the formation of various *1H*-indazole bearing electron withdrawing groups in C3. Several 3-nitro, 3-cyano and alkyl 3-carboxylate *1H*-indazoles were prepared following this one-pot process from the corresponding aromatic azides with good to excellent yields.

Acknowledgements

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Conflicts of interest

There are no conflicts to declare.

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