ChemComm

ROYAL SOCIETY OF CHEMISTRY

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2014, **50**, 8539

Received 8th May 2014,
Accepted 4th June 2014

DOI: 10.1039/c4cc03462g

www.rsc.org/chemcomm

[3+3] annulation of allylic phosphoryl-stabilized carbanions/phosphorus ylides and vinyl azides: a practice strategy for synthesis of polyfunctionalized anilines†

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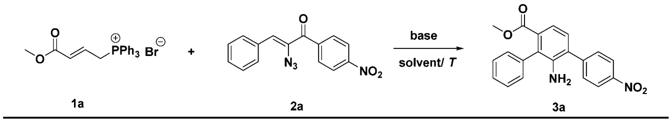
Tandem Michael addition and Witting or Horner–Wadsworth–Emmons olefination initiated [3+3] annulation between vinyl azides and allylic phosphorus ylides or allylic phosphoryl-stabilized carbanions has been developed. This one-pot protocol furnishes highly functionalized anilines in good to excellent yields under mild, room-temperature conditions. A rational mechanism is also proposed.

The aniline skeleton is an intriguing synthetic target because of its abundance in biologically active natural products, pharmaceuticals, pesticides, and dyes.[1,2] In industry, electrophilic nitration of arenes followed by reduction is a key technology for aniline formation though it is limited by essential position directing and a relatively narrow substrate scope.[3] On the other hand, the Buchwald–Hartwig amination reaction has been extensively utilized for generating anilines. These coupling reactions are commonly catalysed by metal and phosphine ligands[4] either using an indirect nitrogen source[5] or by direct amination using ammonia.[6] In addition to these conventional modifications on benzene rings, cross coupling of malononitrile and some activated moieties, such as α-methylene ketones, ynones and nitrostyrenes, is employed for multisubstituted aniline formation.[7] Despite these advances, the control of substituents on the aniline ring, the limited source of the starting materials and the development of milder reaction conditions still remains a challenge. Thus, the development of novel efficient strategies for the construction of polyfunctionalized anilines is highly desirable.

In search of alternatives to the cross-coupling of saturated N-heterocycles, our group and others have reported the use of a vinyl azide as a synthon for the formation of nitrogen-containing heterocycles, such as pyrrolo[1,2-α]pyrazine,[8a] 4-aminopyridines,[8b] pyrazoles,[8c] or other heterocycles.[8d–g] The continued interest in electrophilic reactivity of vinyl azides motivated us to investigate the reactions of vinyl azides with allylic phosphorus ylides or phosphoryl-stabilized carbanions, the latter of which are frequently investigated for their C–C bond formation.[9,10] Herein, a [3+3] cascade transformation is reported under mild reaction conditions, which provides a convenient method for the synthesis of polyfunctionalized anilines. Additionally the exceptional substrate scope of the reaction, which accepts heteroaryl, halogenated, nitro-containing substrates is reported.

Initially, the reaction of crotonate-derived phosphorus ylide (**1a**) and (*Z*)-2-azido-1-(4-nitrophenyl)-3-phenylprop-2-en-1-one (**2a**) was selected as a model to optimize the reaction conditions. Treatment of a mixture of vinyl azide **2a** (1.0 equiv.) and phosphorus ylide **1a** (1.0 equiv.) with EtONa (3.0 equiv.) in i-PrOH at room temperature resulted in the desired aniline **3a** with a conversion of 15% along with unidentified complex mixtures that included phosphazene *via* a Staudinger–Meyer reaction[11] (Table 1, entry 1).

Table 1 Optimization of the reaction conditions[a]



Entry	Base	Solvent	T/°C	Conversion[b]/%
1	EtONa	i-Propanol	rt	15
2	EtONa	*n*-Butanol	rt	18
3	EtONa	CH_3OH	rt	52
4	EtONa	THF	rt	70 (65)[c]
5	EtONa	DMF	rt	26
6	EtONa	CH_3CN	rt	58
7	EtONa	1,4-Dioxane	rt	45
8	EtONa	Toluene	rt	47
9	**EtONa**	**DCM**	**rt**	**87 (85)**[c]
10	Et_3N	DCM	rt	19
11	DBU	DCM	rt	41
12	Cs_2CO_3	DCM	rt	Trace
13	NaOH	DCM	rt	75 (70)[c]

[a] Unless otherwise specified, reactions were performed using **1a** (0.1 mmol) and **2a** (0.1 mmol) in various solvents (1.0 mL) at rt in the presence of the base (0.3 mmol) for 1.0 h. [b] The conversion rate was determined by HPLC, based on the disappearance of the starting vinyl azide (**2a**). [c] Isolated yield.

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† Electronic supplementary information (ESI) available. CCDC 1005572. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4cc03462g

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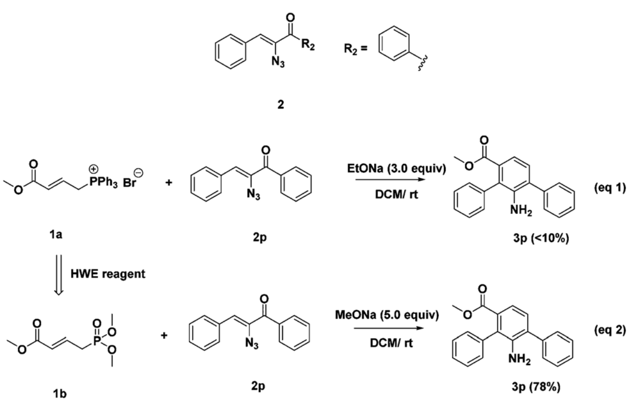
When the reaction was carried out in other protic solvents, the conversion of **3a** was slightly improved to 18% (*n*-butanol) and 52% (CH_3OH), respectively (Table 1, entries 2 and 3). Assessment of the reaction with additional solvents revealed that THF and DCM worked more efficiently, giving **3a** in 65% and 85% yield, respectively (Table 1, entries 4 and 9). The use of other bases, such as Et_3N, DBU and NaOH, were less effective for this transformation (Table 1, entries 10, 11 and 13). In fact when the reaction was carried out in the presence of Cs_2CO_3, only a trace amount of the desired product **3a** could be detected *via* LC-MS (Table 1, entry 12). As shown in Table 1, the highest yield (85%) was obtained when the reaction was performed in DCM at room temperature for 1.0 h using 3.0 equivalents of EtONa (Table 1, entry 9).

This facile annulation reaction encouraged us to explore the generality of the reaction for the synthesis of a variety of polyfunctionalized anilines. A series of substituted vinyl azides (**2a–2o**) and phosphonium ylide (**1a**) were employed as cyclization substrates and subjected to the previously optimized reaction conditions (Table 2).

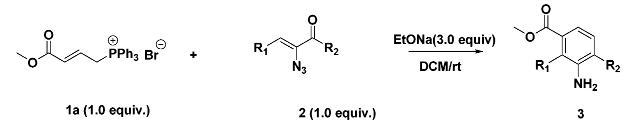
Various vinyl azides **2a–2o**, including those with nitro or halogen moieties, provided the corresponding multifunctionalized anilines **3a–3o** in good to excellent yields. The reaction with vinyl azides, bearing an electron-withdrawing group at the R_1 position, resulted in the corresponding [3+3] annulation products (Table 2, compounds **3f**, **3g**, **3h**, **3i**, **3j**, and **3k**) in good yields. Likewise, the β-electron-donating group substituted vinyl azides are capable of affording the desired anilines, albeit in lower yields (Table 2, compounds **3b**, **3c**, **3d**, **3e**, **3l**, **3m**, **3n** and **3o**). When varying the substitution position on the β-aryl vinyl azides **2**, the corresponding potential steric effects are tolerated by the present method and the desired products are provided in good yields (Table 2, compounds **3f**, **3j** and **3k**).

We then turned our attention towards the scope of substitution of viable R_2 of vinyl azides **2** under the current conditions (Scheme 1). This turned out to be rather challenging (Scheme 1). When the R_2 position of the vinyl azides **2** was substituted with a phenyl group, less than 10% of this transformation occurred under the reaction conditions (Scheme 1, eqn (1)). The poor result was probably due to the weak nucleophilicity of the allylic phosphonium ylide.



Scheme 1 Generality of [3+3] annulation.

Table 2 Scope of vinyl azides 2

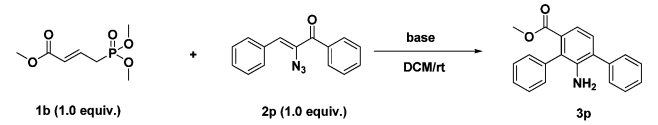


Entry	2	R_1	R_2	Product/isolated yield
1	**2a**	C_6H_5	$4\text{-}NO_2C_6H_5$	**3a** (76%)
2	**2b**	$4\text{-}MeSC_6H_5$		**3b** (68%)
3	**2c**	$4\text{-}MeOC_6H_5$		**3c** (69%)
4	**2d**	$3\text{-}MeC_6H_5$		**3d** (73%)
5	**2e**	$4\text{-}MeC_6H_5$		**3e** (72%)
6	**2f**	$2\text{-}BrC_6H_5$		**3f** (83%)
7	**2g**	$3\text{-}BrC_6H_5$		**3g** (79%)
8	**2h**	$4\text{-}BrC_6H_5$		**3h** (86%)
9	**2i**	$4\text{-}ClC_6H_5$		**3i** (82%)
10	**2j**	$2\text{-}FC_6H_5$		**3j** (78%)
11	**2k**	$2\text{-}Cl\text{-}6\text{-}FC_6H_5$		**3k** (81%)
12	**2l**	$3\text{-}(4\text{-}MeC_6H_5O)C_6H_5$		**3l** (70%)
13	**2m**	$3\text{-}(C_6H_5O)C_6H_5$		**3m** (72%)
14	**2n**	$4\text{-}(C_6H_5O)C_6H_5$		**3n** (71%)
15	**2o**	$4\text{-}(4\text{-}C_6H_5CH_2O)C_6H_5$		**3o** (67%)

To our knowledge, phosphoryl-stabilized carbanions are generally more reactive than phosphorus ylides.[12] We thus examined the use of phosphoryl-stabilized carbanions (**1b**) instead of phosphorus ylides (**1a**) (Scheme 1, eqn (2)) which increased the yield of the desired product to 50% (Table 3, entry 1). The desired product **3p** was obtained in a higher isolated yield (Table 3, entry 2) when MeONa was utilized as the base. Further increasing the amount of base slightly improved the isolated yield (Table 3, entry 3). As shown in Table 3, MeONa and DCM seemed to be the best choice for the reaction of α-phenyl substituted vinyl azide **2p** with phosphoryl-substituted carbanion **1b** providing an excellent yield of 78%.

The results encouraged us to explore the expanded-scope of this annulation. The reaction of methyl (*E*)-4-(dimethoxyphosphoryl) but-2-enoate (**1b**) with various α,β-substituted vinyl azides (**2**) under the standard reaction conditions (given in Table 3) gave the multisubstituted anilines (**3**) in good to excellent yields (Table 4, isolated yields >70%). Both electron-rich and -deficient aryl groups at the R_2 position were tolerated in this annulation. In contrast, when α-tributylcarbonyl-substituted vinyl azide **2x** was reacted with **1b**, only a trace amount of the corresponding aniline **3x** was observed *via* LC-MS. Likewise, when

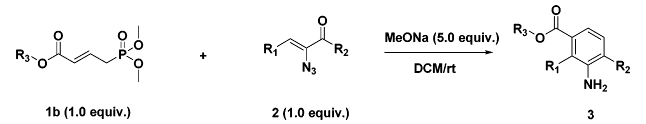
Table 3 Optimization of the reaction conditions[a]



Entry	Base	Equivalent	Solvent	Conversion[b]/%
1	EtONa	3.0	DCM	56 (50)[c]
2	MeONa	3.0	DCM	75 (70)[c]
3	MeONa	5.0	DCM	83 (78)[c]

[a] Reactions were performed using **1b** (0.1 mmol) and **2a** (0.1 mmol) in various solvents (1.0 mL) at rt in the presence of the base for 1.0 h. [b] The conversion rate was determined by HPLC, based on the disappearance of the starting vinyl azide (**2a**). [c] Isolated yield.

Table 4 Generality of [3+3] annulation of vinyl azides with allylic phosphoryl-stabilized carbanions



Entry	2	R$_1$	R$_2$	Product/isolated yield
1	**2a**	C$_6$H$_5$	4-NO$_2$C$_6$H$_5$	**3a** (85%)
1	**2p**	C$_6$H$_5$	C$_6$H$_5$	**3p** (78%)
2	**2q**	2-BrC$_6$H$_5$	C$_6$H$_5$	**3q** (79%)
3	**2r**	3-BrC$_6$H$_5$	C$_6$H$_5$	**3r** (80%)
4	**2s**	4-BrC$_6$H$_5$	C$_6$H$_5$	**3s** (83%)
5	**2t**	2-Pyridinyl	C$_6$H$_5$	**3t** (65%)
6	**2u**	2-Furyl	C$_6$H$_5$	**3u** (70%)
7	**2v**	C$_6$H$_5$	4-MeC$_6$H$_5$	**3v** (76%)
8	**2w**	C$_6$H$_5$	4-BrC$_6$H$_5$	**3w** (83%)
9	**2x**	C$_6$H$_5$	C(CH$_3$)$_3$	**3x** (trace)
10	**2y**	C$_6$H$_5$	OEt	**3y** (0%)
11	**2z**	C$_6$H$_5$	H	**3z** (0%)

the α-ester substituted vinyl azide **2y** was employed, no desired aniline **3y** was observed. These results suggested that the poor electrophilicity of these vinyl azides did not enable a HWE-olefination to form the desired anilines. While, the strong reactivity of the aldehyde group at the α-position of vinyl azide **2z** favoured an intermolecular HWE olefination over a [3+3] annulation under the optimization reaction conditions. In general though the tandem reaction showed broad tolerance for various R$_1$ groups of vinyl azides, selected substrates bearing phenyl (**2p**, **2v** and **2w**), electron-deficient aryl (**2q**, **2r** and **2s**), and heteroaryl (**2t** and **2u**) at R$_1$ groups reacted efficiently with **1b** to provide the corresponding anilines (**3p**–**3u**) in high yields at room temperature for 1.0 h.

The structures of the polyfunctionalized anilines were characterized by ^{1}H NMR, ^{13}C NMR and HRMS. The structures of one representative compound **3c** were proved by X-ray crystal structural analysis as shown in Fig. 1 (CCDC 1005572).

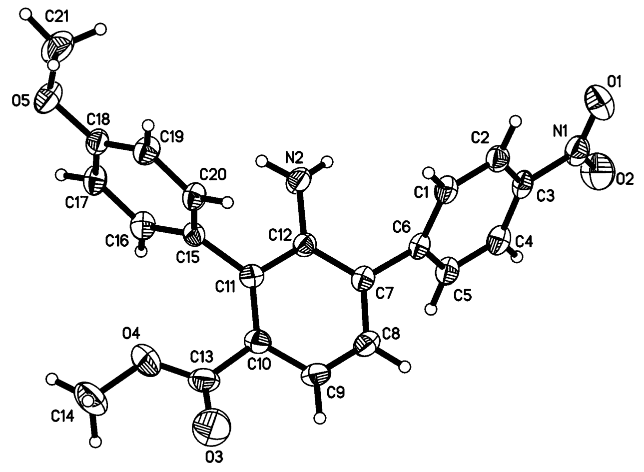
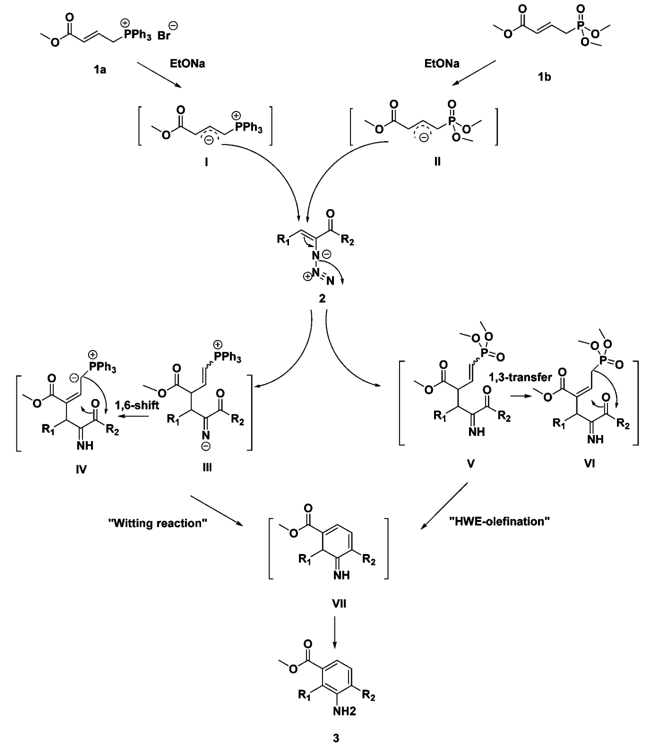


Fig. 1 X-Ray crystal structure of **3c**.



Scheme 2 Proposed mechanism for the annulation.

The tandem reaction sequence outlined in Scheme 2 was proposed to explain this facile transformation. Nucleophilic attack of ylide **1a** or phosphoryl-stabilized carbanion **1b** with vinyl azides **2** initiates the formation of adduct **III** or **V** in the presence of base. Adduct **III** exclusively undergoes 1,6-proton shift to convert to intermediate **IV**, while intermediate **VI** is formed from adduct **V** *via* 1, 3-proton transfer. The annulation process is followed by an intramolecular Witting or HWE olefination and subsequent proton transfer to afford the corresponding aniline **3**.

In summary, a base-promoted [3+3] annulation between allylic phosphoryl-stabilized carbanions or phosphorus ylides with vinyl azides was developed under mild, room temperature conditions. This facile reaction allows construction of polyfunctionalized anilines in good yields. Both the substituents and positions on the anilines can be easily controlled by choosing appropriate and accessible starting materials. A rational mechanism was also proposed. It is anticipated that the present annulation is potentially useful for synthesis of biologically and medicinally important anilines.

This research was supported by the National Natural Science Foundation of China (No. 81273356), the Natural Science Foundation of Zhejiang Province (No. Z2110655), the Program for Zhejiang Leading Team of S&T Innovation, and Alzheimer's & Aging Research Centre, USA. And we appreciate Marc Giulianotti (Torrey Pines Institute for Molecular Studies, USA) for critical reading of the manuscript.

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