Unusual Sequential Base-Promoted Annulation/Palladium-Catalysed Cascade 1,5-enyne Arylation and Vinylation of α-Propargylaminohydrazones

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1,2-Diazabuta-1,3-dienes represent versatile building blocks in organic synthesis because they offer an easy access to a wide variety of heterocyclic compounds by 1,4-conjugate addition and subsequent cyclization reaction.[1] Moreover, the Michael's adducts on 1,2-diazabuta-1,3-diene system may act as nitrogen ligands[2] for transition-metal catalysts leading to unusual reaction pathways.[3] Among other Michael's adducts of amines on 1,2-diazabuta-1,3-dienes can undergo divergent copper$^{I/II}$ promoted annulation reactions to accomplish the regiocontrolled synthesis of functionalised imidazolines/imidazoles, whereas the base promoted cyclisation provide both 1-substituted and 1-unsubstituted-4-aminocarbonyl-1H-pyrazol-5(2H)-ones.[4]

An impressive variety of metal-catalysed reactions of enynes involving a broad range of early and late transition metals have been proven to be of paramount interest for the synthesis of functionalized carbo/heterocycles.[5] The classes of reactions that involve metal-catalysed functionalisation of enynes include among others cycloisomerisation,[6] reductive cyclisation,[7] bismetallative cyclisation,[8] carbonylative cyclisations,[9] and dimerisation/cyclisation.[10] One-pot domino reactions of enynes provide valuable procedure for an easy access to five- and six-membered heterocycles containing a 1,3-diene structure that can lead to bicyclic compounds via in situ Diels-Alder reactions.[11]

Domino reactions are emerging as powerful strategies in modern synthetic organic chemistry and the discovery of new reaction sequences able to produce valuable elaborated compounds constitutes a challenge both from academic and industrial points of view.[12]

Interestingly, the α-propargylaminohydrazone adducts **1a-c,** containing a 1,4-diazo-1,6-azenyne system, turned out to be useful substrates for further metal-catalyzed processes.

In this context we decided to investigate in detail the palladium-catalysed arylation and vinylation reactions of α-propargylaminohydrazones and here we report new efficient synthetic methodology for the preparation of (Z)-6-arylidene/vinylidene-6a-methyl,1,5,6a-terahydro-2H-pyrrolo[3,2-c]pyrazol-3-ones through highly remarkable sequential base-promoted annulation/palladium catalyzed domino 1,5-enyne arylation and vinylation reactions.

Indeed, the treatment of the α-propargylaminohydrazones **1a-c** with anhydrous piperidine in the presence of aryl iodide/triflate derivatives **2a-h** and Pd(OAc)$_2$/DPPF catalytic system

accomplished the synthesis of (*Z*)-6-arylidene/vinylidene-6a-methyl,1,5,6a-terahydro-2*H*-pyrrolo[3,2-*c*]pyrazol-3-ones **3a-h**, in good yields (Scheme 1, Table 1).
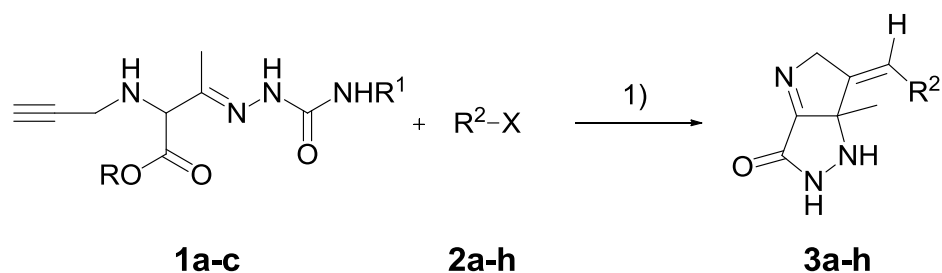
Scheme 1. Reagents and conditions: 1) Pd(OAc)$_2$, DPPF, piperidine, room temperature, 24 h; DPPF = 1,1'-bis(diphenylphosphino)ferrocene. Spectroscopic data of the new compounds can be found in the supporting information.

Table 1. Compounds **1-3**.

1	R	R^1	2	Structure	3	Structure	Yield[a] (%)
a	Me	H	**a**		**a**		67
b	Et	H	**b**		**b**		68
c	Me	Ph	**c**		**c**		67
			d		**d**		64
			e		**e**		62
			f		**f**		66
			g		**g**		64
			h		**h**		65

The structure of compounds **3** was demonstrated by mono (^{1}H, ^{13}C) and bidimensional (COSY, HETCOR, NOESY) NMR spectra analysis and by mass spectroscopy. In particular, NOESY experiments clearly demonstrated that the geometry of the exocyclic double bond is *Z* for all synthesized compounds **3a-h**, moreover ^{1}H and ^{13}C-NMR signals of the vinyl substituted pyrrolo[3,2-*c*]pyrazol-3-ones **3e-h** are split by the presence of more isomers.

Indeed, the absence of n.O.e. interaction between the olefinic protons on the exocyclic double bond and on the cyclohexene ring in **3e** was explained performing a conformational search[13] at AM1[14] semi-empirical level in order to evaluate the conformational energies of **3e**. In particular, the obtained results show that the conformers with the lower steric energies have spatial arrangements which are in agreement with the observed n.O.e. interactions. Moreover, the analysis of all the observed minima show that there is only one local minimum with a spatial arrangement compatible with a n.O.e. interaction between the two olefinic protons (< 3 Å apart), however his steric energy is about 10 kJmol^{-1} higher than the global minimum structure.

A reasonable rationale for the production of **3** is depicted in Scheme 2. Likely, the reaction involves the formation of the 1-aminocarbonyl-1*H*-pyrazol-5(2*H*)-ones **4** derivatives obtained by piperidine promoted annulation reaction of **1a-c**, according to our previous findings.[4b] The smooth solvolytic cleavage of the group linked to the nitrogen atom in position 1 gives 5-methyl-4-propen-2-ynylamino-1,2-dihydro-pyrazol-3-one **5**. In fact, ureas **6** were isolated as reaction side products. Then, the formation of **3a-h** is achieved through the palladium-catalysed domino arylation or vinylation/carbocyclization of **5**. Thus, the regioselective *syn* addition of the σ-vinyl/arylpalladium complex on the triple bond of **7** afford the σ-vinylpalladium intermediate **8** which may evolve by a carbocyclopalladation step to the intermediate **9**. Finally, the elimination of HPdX from **9** produces stereopecifically the (*Z*)-6-arylidene/vinylidene-6a-methyl,1,5,6a-terahydro-2*H*-pyrrolo[3,2-*c*]pyrazol-3-ones derivatives **3** and regenerates the active catalyst. The stereochemical outcome of the reaction is in agreement with the sequence illustrated in the Scheme 2 and with the results obtained in bismetallative palladium-catalysed cyclization of enynes.[8]
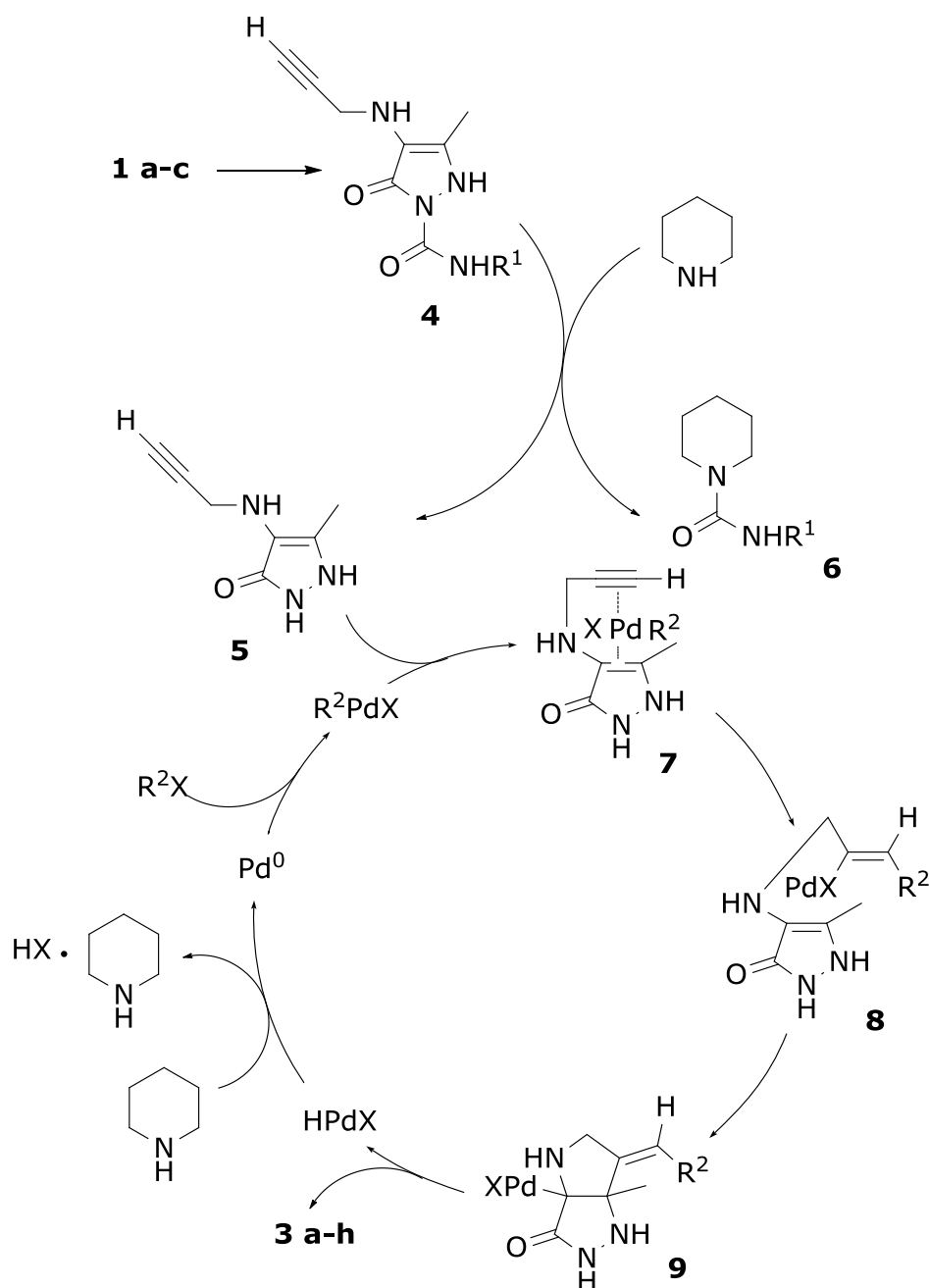
Scheme 2. A plausible catalytic cycle for 1,5,6a-terahydro-2*H*-pyrrolo[3,2-*c*]pyrazol-3-ones formation.

Although the Pd(II)-catalysed intramolecular cyclization of enynes has been utilised for the preparation various five-membered ring systems,[6a,15] to the best of our knowledge the sequential palladium-catalysed reaction here reported represents the first example of domino palladium catalysed intermolecular arylation/vinylation-intramolecular[16] carbopalladation process of 1,5-enyne derivative leading to fused heterocycles through a regioselective 5-*endo-dig* annulation reaction followed by β-hydride elimination with cleavage of N-H bond. Only few examples involving σ-aryl/vinyl palladium complexes to achieve intramolecular-intramolecular-intramolecular-intermolecular[17] cascade carbopalladation, and domino palladium-catalysed

intermolecular arylation/vinylation-intramolecular[14] carbopalladation process of 1,6- or 1,7-enynes have been reported.

In conclusion, we have developed a new efficient Pd-catalyzed ene-type carbocyclization and current efforts are now focused on these and related substrates in order to access the synthetic potential of this procedure.

Experimental section

To a nitrogen flushed solution of α-aminohydrazones **1a-c** (1 mmol) in dry piperidine (6 ml) were added the appropriate halides or triflates **2a-h** (1 mmol), Pd(OAc)$_2$ (11.22 mg, 0.05 mmol), and DPPF (27.72 mg, 0.05 mmol). The reaction mixture was stirred at room temperature for 24 h, poured into HCl 0.1M (100 ml) and extracted twice with ethyl acetate. The organic layer, dried over Na$_2$SO$_4$, was evaporated to dryness and the crude purified by flash chromatography over silica gel. Elution with petroleum ether/ethyl acetate mixtures afforded pure **3a-h**.

3a: m.p. 139.7-141.9 °C ; IR (KBr): ν = 3360, 3186, 1718, 1682, 1560 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$, 25°C): δ = 1.98 (s, 3H; CH$_3$), 2.58 (s, 3H; CH$_3$CO), 2.93 (brs, 1H, D$_2$O-exch.; NH), 4.05 (dd, ^{2}J(H,H) = 15 Hz, ^{4}J(H,H) = 2 Hz, 1H; CH$_2$), 4.35 (dd, ^{2}J(H,H) = 15 Hz, ^{4}J(H,H) = 2 Hz, 1H; CH$_2$), 6.70 (t, ^{4}J(H,H) = 2 Hz, 1H; =CH), 7.32 (d, ^{3}J(H,H) = 7.8 Hz, 2H; arom.), 7.88 (d, ^{3}J(H,H) = 7.8 Hz, 2H; arom.), 8.82 (brs, 1H, D$_2$O-exch.; NH); ^{13}C NMR (75.4 MHz, CDCl$_3$, 25°C): δ = 13.9 (CH$_3$), 26.9 (CH$_3$CO), 54.9 (CH$_2$), 78.2 (quat. C$_{sp3}$), 126.2 (C$_{sp2}$H, 2C; arom.), 129.3 (C$_{sp2}$H, 2C; arom.), 134.6 (=C$_{sp2}$H), 137.0 (quat. C$_{sp2}$), 137.2, (quat. C$_{sp2}$), 138.0, (quat. C$_{sp2}$), 164.1 (C=N), 178.1 (C=O), 197.8 (C=O); MS (70 eV): m/z (%): 269 (100) [M$^+$]; Anal. Calcd. for C$_{17}$H$_{15}$N$_3$O: C, 73.62; H, 5.45; N, 15.15. Found: C, 73.79; H, 5.57; N, 14.85.

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