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Regioselectivity of the Chan–Lam coupling of ambident nitropyrazoles with *trans*-styrylboronic acid

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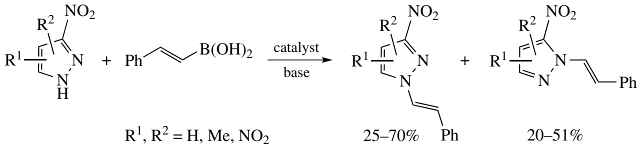
Regioselectivity of the Chan–Lam coupling of ambident nitropyrazoles with *trans*-styrylboronic acid depends on the base and catalyst nature and can vary the N(1)/N(2)-isomer ratio from ~2 : 1 to ~1 : 2. 2-Methyl-4-nitro- and 2,4-dinitroimidazoles are unreactive in this reaction. The structure of N(1)/N(2) isomers was elucidated by NOE measurements and by the comparison of experimental and DFT calculated ^{13}C NMR chemical shifts.



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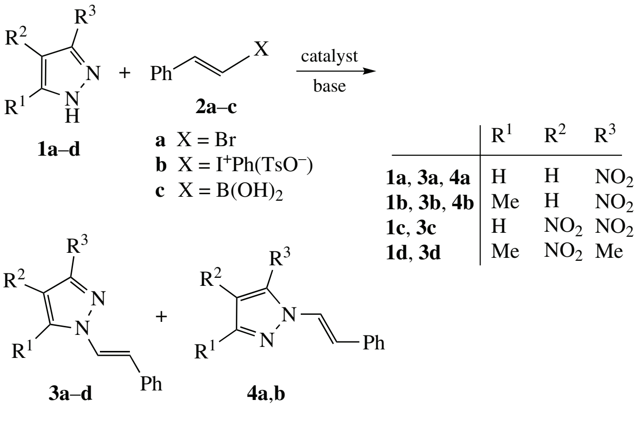
N-Modified nitroazoles are valuable compounds due to their high biological and pharmacological activity and synthetic applications.[1] In particular, some nitro-*N*-vinylazoles possess good antimicrobial and antyinflammatory activity[2] and are applied for synthesis of other classes of heterocyclic compounds such as nucleosides and nucleotides[3] and N-fused heterocycles.[4]

Classical methods for the synthesis of nitro-*N*-vinylazoles are typically based on multistage chemical processes.[3(b),4(a)] From the practical point of view, only the direct regioselective N-modification of ambident anions of nitroazoles with available agents can be optimal.[5] At the same time, we could not find any modern procedure for the N-vinylation of nitroazoles employing transition metal catalysis.

In principle, catalytic N-vinylation of non-symmetrical nitropyrazoles with various vinyl-containing reagents can give two isomers (Scheme 1).

Initially, we tried to perform direct coupling of available 3-nitropyrazole **1a** with *trans*-styryl bromide **2a** in the presence of CuI under conditions described by Taillefer.[6] Very low total yield of products **3a**, **4a** was observed both in MeCN and DMF (Table 1, entry 1).



Scheme 1 For details and yields, see Tables 1 and 2.

Table 1 Optimization of N-vinylation of 3-nitropyrazole **1a** with *trans*-styryl-containing reactants **2a**–**c**.

Entry	Vinylation reactant	Catalyst[a]	Solvent	T/°C	t/h	Base, additive	Atmo-sphere	Yield of **3a** (%)[b]	Yield of **4a** (%)[b]	N(1)/N(2) (**3a** : **4a**) ratio[c]
1	**2a**	CuI	MeCN, DMF	80	6	Cs_2CO_3	Ar	very low	very low	–
2	**2b**	Pd[d]	MeCN	20	6	Al_2O_3 basic	Ar	traces	traces	–
3	**2b**	CuI	CH_2Cl_2	20	6	$[Cu_2(TMEDA)_2(OH)_2]Cl_2$	Ar	traces	traces	–
4	**2b**	CuI	MeCN	80 (MW)	0.25	DBU	Ar	traces	traces	–
5	**2c**	CuCl	MeOH	65	6	NaOH	air	traces[a]	traces	–
6	**2c**	CuCl	CH_2Cl_2	20	6	Py or Et_3N	air	very low[e]	very low	
7	**2c**	$CuSO_4$	CH_2Cl_2	20	24	Py	O_2	42	20	~2.1
8	**2c**	$Cu(OAc)_2$	CH_2Cl_2	20	24	Py	O_2	40[f]	20	~2.0
9	**2c**	$Cu(OTf)_2 \cdot PhH$	CH_2Cl_2	20	24	Py	O_2	45	22	~2.1
10	**2c**	$[Cu_2(TMEDA)_2(OH)_2]Cl_2$	CH_2Cl_2	20	24	Py, MS 4 Å	O_2	31	30	~0.9
11	**2c**	$[Cu_2(TMEDA)_2(OH)_2]Cl_2$	CH_2Cl_2	20	24	K_2CO_3	O_2	25	51	~0.5

[a] 10 mol% of [Cu] catalyst. [b] Isolated yield after TLC. [c] Calculated from ^{1}H NMR data of the reaction mixtures purified by flash chromatography. [d] Pd/Al_2O_3 basic. [e] Up to 20% of 1,4-diphenylbutadiene formed. [f] *trans*-Styryl acetate (~3%) was found in the reaction mixture.

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