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

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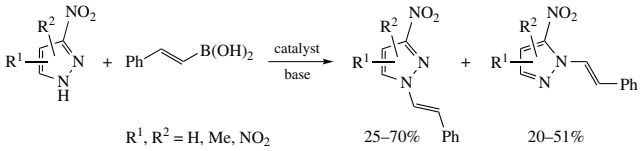
Regioselectivity of the Chan–Lam coupling of ambident nitropyrazoles with *trans*-styrylboronic acid depends on the base and catalyst nature and can vary the N(1)/N(2)-isomer ratio from ~2 : 1 to ~1 : 2. 2-Methyl-4-nitro- and 2,4-dinitroimidazoles are unreactive in this reaction. The structure of N(1)/N(2)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



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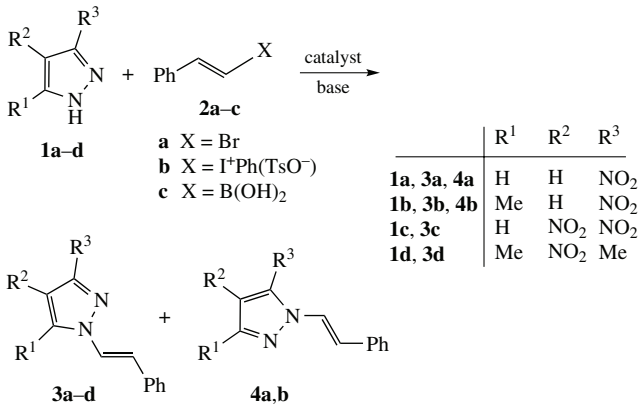
N-Modified nitroazoles are valuable compounds due to their high biological and pharmacological activity and synthetic applications.[1] In particular, some nitro-*N*-vinylazoles possess good antimicrobial and antyinflammatory activity[2] and are applied for synthesis of other classes of heterocyclic compounds 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	Atmosphere	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**	$Cu(OTf)_2$·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.

Table 2 Copper-catalyzed N-vinylation of nitroazoles with *trans*-styrylboronic acid.[a]

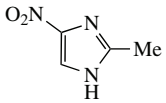
Entry	Substrate[b]	p*Ka*[c]	Catalyst	Base	N(1)-product [yield (%)][d]	N(2)-product [yield (%)][d]	N(1)/N(2) (**3**:**4**) ratio[e]
1	**1a**	9.81	$CuSO_4$	Py	**3a** (42)	**4a** (20)	~2.1
2	**1a**	9.81	$[Cu_2(TMEDA)_2(OH)_2]Cl_2$	K_2CO_3	**3a** (25)	**4a** (51)	~0.5
3	**1b**	10.25	$CuSO_4$	Py	**3b** (38)	**4b** (25)	~1.5
4	**1b**	10.25	$[Cu_2(TMEDA)_2(OH)_2]Cl_2$	K_2CO_3	**3b** (24)	**4b** (35)	~0.7
5	**1c**	5.48	$[Cu_2(TMEDA)_2(OH)_2]Cl_2$ or $CuSO_4$	Py or K_2CO_3	**3c** (~50)		–
6	**1d**	10.65	$[Cu_2(TMEDA)_2(OH)_2]Cl_2$	K_2CO_3	**3d** (~70)		–

[a] Conditions: CH_2Cl_2, 10 mol% [Cu] and base, O_2 atmosphere, room temperature, 24 h. [b] Nitroazoles were kindly provided by the Professor I. L. Dalinger from the N. D. Zelinsly Iinstitute of Organic Chemistry. [c] Ref. 11. [d] Isolated yield after TLC. [e] Calculated from ^{1}H NMR data of the reaction mixtures purified by flash chromatography.

Taking into account our interest to regioselective catalytic N-modification of ambident nitrogen heterocycles with iodonium salts,[7] first we tested vinyliodonium salts **2b** used previously in Pd- or Cu-catalyzed N-vinylation of symmetric benzotriazoles. Unfortunately, the desired products were not formed both under mild and harsh reaction conditions[7(c)] (see Table 1, entries 2–4).

Recently, the Chan–Lam coupling became popular in the carbon-element bond formation.[8] The first experiment in MeOH using the Suwinsky[9] conditions for arylation of nitroazoles with arylboronic acids **2c** was non-effective, as we detected only traces of products (see Table 1, entry 5). With CH_2Cl_2 as the solvent, organic base and CuCl as the catalyst in air atmosphere, the reaction gave very low overall yield of products **3a** and **4a** (entry 6). The best results were achieved when oxygen gas from balloon was applied as the oxidant while other conditions were the same (entry 7). In this experiment, the ratio of N(1)/N(2)-isomers **3a** and **4a** was near 2 : 1. Variation of copper salts practically did not affect the yield and the ratio of reaction products, however in the case of $Cu(OAc)_2$, little (~3%) *trans*-styryl acetate was detected (entries 8 and 9). When Collman's complex[10] $[Cu_2(TMEDA)_2(OH)_2]Cl_2$ was tried as the catalyst with Py or Et_3N as the bases, almost equal amounts of N(1) and N(2)-isomers were obtained (entry 10). The use of K_2CO_3 as the base resulted in practically full inversion of vinylation regioselectivity. The results of optimization were applied to vinylation of some other nitroazoles **1a–d** (see Scheme 1, Table 2).

As mentioned above, we observed full inversion of regioselectivity when replacing the $CuSO_4$ catalyst with Collman's complex and Py with K_2CO_3 as the base (see Table 2, entries 1 and 2). In the case of 3-methyl-5-nitropyrazole **1b**, the increase in the yield of the second isomer also occurred (entries 3 and 4). However, in the case of ambident 3,4-dinitropyrazole **1c** only one isomer was formed (entry 5).[12] Obviously, 3,5-dimetyl-4-nitropyrazole **1d** gave the only possible isomer (entry 6). Unexpectedly, the vinylation of 2-methyl-4-nitroimidazole **5** was not successful, whereas the failure to vinylate 2,4-dinitropyrazole **6** was probably due to poor nucleophilicity of its conjugated anion.



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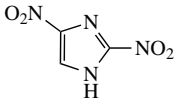

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Two approaches were used to elucidate the structure of isomeric N(1)- and N(2)-vinylation products **3** and **4** of ambident nitropyrazoles, *viz.* NOE measurements and the correlation of the experimental and computed ^{13}C NMR chemical shifts.

Figure 1 illustrates the observed NOE enhancements of the selected proton signals (indicated by red arrow) upon the irradiation of the proton from which the arrow starts. Assignment of the signals of the vinylic protons was done according to their line widths since the slightly broader signal should belong to vinylic proton adjacent to phenyl ring (line broadening results from the unresolved long-range spin–spin coupling with phenyl protons[13]). For pyrazole **3b**, a 2.6% NOE was observed on the vinylic proton adjacent to pyrazole nitrogen (see Figure 1) upon the irradiation of Me group. It shows that Me group occupies the position 5, nearest to vinylic hydrogen. As a further confirmation, NOE was measured for 3,5-dimethyl derivative **3d**. In this case, of the two methyl signals only the irradiation of the lower-field one produced NOE on the vinylic proton.

In the ^{1}H NMR spectra of vinylated pyrazoles **3a** and **3c**, the irradiation of H-5 proton in the pyrazole ring produced NOE on both vinylic protons (see Figure 1). Besides proving the 3-NO_2 *vs.* 5-NO_2 substitution pattern, this also shows that 5-unsubstituted 1-[(*E*)-2-phenylvinyl]-1*H*-pyrazoles exist as a mixture of *s-cis*- and *s-trans*-rotamers, which is in agreement with published data.[14] On the other hand, 5-substituted 1-[(*E*)-2-phenylvinyl]-1*H*-pyrazoles exist as essentially one, namely *s-cis*-rotamer, since no NOE is observed on the vinylic proton nearest to phenyl group.

The structure of nitropyrazole vinylation products **3** and **4** was independently confirmed by quantum chemical DFT

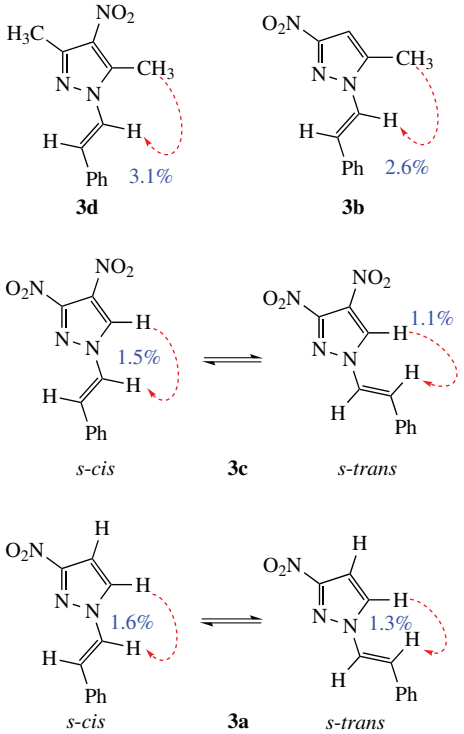

Figure 1 NOE values for the 5-substituted and 5-unsubstituted 1-[(*E*)-2-phenylvinyl]-1*H*-pyrazoles.

calculation of ^{13}C NMR chemical shifts ($\delta^{13}C$). GIAO NMR calculations were performed at CPCM/mPW1PW91/Def2-TZVP level for B3LYP optimized geometries using ORCA program package.[15] Similar level of theory has previously shown good performance for the calculation of NMR-shielding in various classes of organic compounds.[16]

The calculations revealed that 3-nitro-1-[(*E*)-2-phenylvinyl]-1*H*-pyrazoles **3** were 1.7–6.3 kcal mol^{-1} more stable than their 5-nitro-isomers **4**. *s-cis*-Rotamers were always found to be more stable than *s-trans* ones, however the energy differences for compounds **3a** (0.4 kcal mol^{-1}) and **3c** (0.6 kcal mol^{-1}) were very small, which means that both rotamers have to be considered and the $\delta(^{13}C)$ calculated as Boltzmann averaged values for *s-cis*- and *s-trans*-rotamers (see Online Supplementary Materials, Table S1). For other four nitropyrazoles, the *s-cis*-rotamer was calculated to be at least 2 kcal mol^{-1} more stable than the *s-trans* one and only the former was taken for NMR calculation. The conclusion on rotamer stability is also in accord with the results of NOE measurements.

There is an excellent agreement ($R^2 = 0.9991$) between the calculated and the experimental $\delta(^{13}C)$ values with the mean absolute error of 1.64 ppm and maximum error of 5.17 ppm for the whole set of $\delta(^{13}C)$ for all studied compounds (see Online Supplementary Materials, Figure S25). If the calculated $\delta(^{13}C)$ are scaled according to the linear fit equation, the mean and maximum errors are lowered to 1.15 and 3.06 ppm, respectively. However, if the $\delta(^{13}C)$ calculated for 5-NO_2 isomer **4** are plotted against the experimental $\delta(^{13}C)$ for 3-NO_2 isomer **3**, the correlation deteriorates (compare Figures S26 and S27). Especially large error is seen for lower-field pyrazole CH signal, *i.e*. C^5 in 3-nitro- and C^3 in 5-nitro-isomer. This large difference in chemical shielding can be easily explained, since in 5-nitropyrazole isomer this carbon has imine character (C=N, pyridine-type), while in 3-nitropyrazole it resembles one in pyrrole (enamine character, =C–N). There are also large differences in $\delta(^{13}C)$ of *C*-NO_2 signals in 5-nitro (144–146 ppm) and 3-nitro isomers (155–157 ppm) which have the same origin and are correctly reproduced by the calculation.

In conclusion, the Chan–Lam coupling can be used for obtaining *N*-vinyl derivatives of ambident and non-ambident nitropyrazoles. Their ^{13}C NMR spectra in combination with DFT calculation of $\delta(^{13}C)$ and NOE measurements provide adequate criteria to distinguish between isomeric 3-nitro- and 5-nitro-1-[(*E*)-2-phenylvinyl]pyrazole structures.

High resolution mass spectra were recorded at the Department of Structural Studies of N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2020.03.018.

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