

# Intramolecular Cyclization of Vinyldiazoacetates as a Versatile Route to Substituted Pyrazoles

Denis Drikermann, Valerie Kerndl, Helmar Görls, Ivan Vilotijevic\*

Institute of Organic Chemistry and Macromolecular Chemistry, Friedrich Schiller University Jena,  
Humboldtstr. 10, 07743 Jena, Germany.

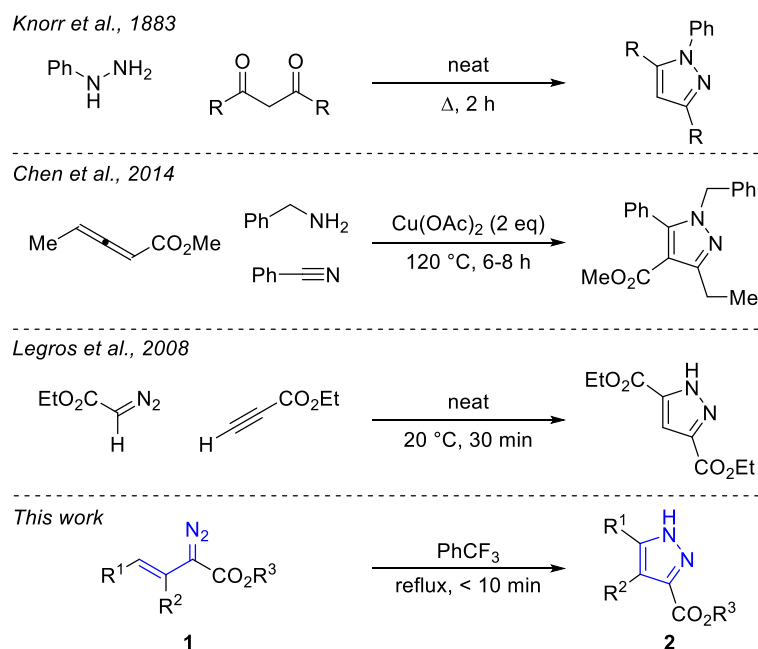
E-mail: [ivan.vilotijevic@uni-jena.de](mailto:ivan.vilotijevic@uni-jena.de)

**Abstract:** Vinyldiazo compounds undergo a thermal electrocyclization to form pyrazoles in yields of up to 95%. The reactions are operationally simple, use readily available starting materials, require no intervention of a catalyst, and enable the synthesis of mono-, di- and tri-substituted pyrazoles. With the ability to produce highly substituted pyrazole and the flexibility in installing various types of substituents, this method constitutes a new entry to this valuable heterocyclic scaffold of interest in all branches of chemical industry.

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First prepared by Ludwig Knorr in 1883,<sup>1</sup> pyrazoles and their derivatives have been a common structural motif in chemical, agricultural, pharmaceutical and related industries. This heterocyclic scaffold is a part of numerous biologically active molecules with anti-inflammatory, anti-psychotic, anti-depressant and anti-cancer activity.<sup>2</sup> Beside the condensation of hydrazine derivatives with 1,3-dicarbonyl compounds, similar to Knorr's synthesis,<sup>3</sup> numerous synthetic pathways to pyrazoles have been reported.<sup>4</sup> Recent examples include multicomponent reactions,<sup>5</sup> dipolar cycloadditions of diazo compounds<sup>6</sup>, nitrile imines<sup>7</sup> or azomethine imines<sup>8</sup> with alkynes and others (Scheme 1). Although numerous synthetic routes to pyrazoles exist, regioselective synthesis of densely functionalized pyrazoles remains a challenge.

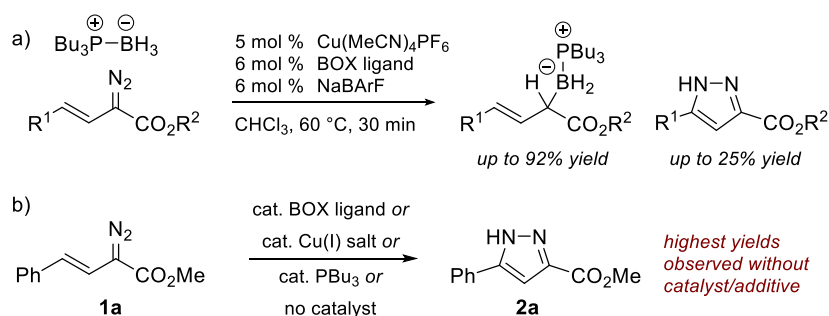
Cyclization of vinyldiazoacetates could provide an alternative general path for direct synthesis of pyrazoles with a variety of substituents present on all three carbon atoms of pyrazole (Scheme 1). The feasibility of this approach is supported by the previous reports of cyclization of vinyldiazo compounds and the observation of pyrazoles as side products in Lewis acid, Rh(II), Cu(II), Co(II), Au(I), Ag(I) or base catalyzed reactions that utilize vinyldiazoacetates as starting materials.<sup>9</sup> The latter observations were echoed in our work on catalytic insertions of metal carbenoids derived from vinyldiazoacetates into heteroatom-H bonds where pyrazoles were observed as side products alongside the desired allylic boranes (Scheme 2a).<sup>10</sup> Considering the ease of access to various vinyldiazoacetates via diazo-transfer to  $\beta,\gamma$ -unsaturated esters, we hypothesized that the cyclization of these compounds would allow for an operationally simple and general entry to highly substituted pyrazoles. With this hypothesis, we set off to identify the catalysts that would promote such cyclizations, establish the procedure for the synthesis of differentially substituted pyrazoles and systematically study the reaction scope.



**Scheme 1** Selected previous work on synthesis of pyrazoles and outline of the strategy to prepare pyrazoles via cyclization of vinyldiazo compounds.

Keeping in mind the observation that pyrazoles are formed as side products in the presence of Cu(I) catalyst, BOX ligands and phosphine-borane adduct (Scheme 2a), attempts were made to use each of these as a catalyst or a reagent individually. Cu(I) salts, BOX ligands and nucleophilic phosphines<sup>11</sup> all proved to be less efficient than the simple thermally induced cyclization of the vinyldiazoacetate **1a** (Scheme 2b).

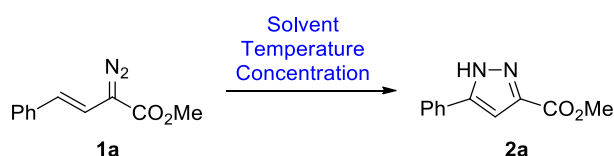
With a better understanding of the fact that these reactions proceed as thermally promoted cyclizations of the vinyldiazo 1,5-dipole and require no intervention of a catalysts, focus was shifted to optimization of the reaction conditions: identity of the solvent, temperature, concentration and the time required for full conversion. Considering the charge separation in the starting vinyldiazoacetate and the redistribution of electron density in the transition states for the cyclization, predicting the solvent effects was not intuitive.



**Scheme 2** a) The observation of the cyclization of vinyldiazoacetates during Cu(I) catalyzed B-H insertions. b) Initial search for catalysts to promote cyclization of vinyldiazoacetates.

Standard laboratory solvents and solvent mixtures have been employed at refluxing temperatures in the search for the optimal medium for the rearrangement (Table 1). Formation of pyrazole from the corresponding vinyldiazoacetate was observed in all tested solvents. Non-polar solvents and polar protic solvents afforded the desired products in moderate to good yields (Entries 1-5). Better yields were generally observed in polar, aprotic solvents (Entries 6-13) with pyridine, 2,6-lutidine and trifluorotoluene giving the highest yields of 91%, 87% and 81% respectively. Reactions in trifluorotoluene proceeded with significantly higher rate, requiring less than 10 minutes to complete and allowing for product to directly precipitate out of the solution, which is why trifluorotoluene was used in further optimization. Somewhat counterintuitively, increasing the concentration of vinyldiazoacetate in the reaction mixture to 1.2 M led to an improvement of the isolated yield to 89% with reaction times of less than 10 minutes which suggests that the intramolecular cyclization readily outperforms any possible bimolecular pathways.

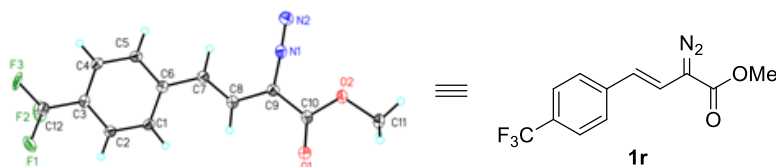
**Table 1** Optimization of the reaction conditions: solvent, temperature and concentration.



Entry	Solvent	[1a] [mol/L]	T [°C]	Yield [%]
1	THF	0.25	66	59
2	PhMe	0.25	111	73
3	DCE	0.25	84	70
4	MeOH	0.25	65	46
5	<i>t</i> BuOH	0.25	83	63
6	DMSO	0.25	120	75
7	PhMe/DMPU (1 : 1)	0.25	120	66
8	DMPU	0.25	120	68
9	C <sub>6</sub> F <sub>6</sub>	0.25	81	75
10	PhCF <sub>3</sub>	0.25	102	81
11	<i>PhCF</i> <sub>3</sub>	1.20	102	89
12	C <sub>6</sub> H <sub>5</sub> N	0.25	115	91
13	2,6-Lutidine	0.25	144	87

The vinyldiazoacetates required for the studies of reaction scope could be easily prepared via Regitz-diazotransfer<sup>12</sup> to the corresponding  $\beta,\gamma$ -unsaturated ester using DBU as base and *p*-ABSA as diazotransfer reagent. To address any ambiguity about the structure of the resulting vinyldiazo compound with respect to the possibility of diazotransfer to C2 or to C4 with transposition of the double bond, a heavier crystalline analog of the diazo transfer product **1r** was subjected to X-ray crystallography to determine that the only observed and isolated isomer was indeed the desired aryl-substituted vinyldiazoacetate (Scheme 3). This was further corroborated by the alternative path to the vinyldiazoacetate **1x** via the palladium-catalyzed coupling of (*E*)-(2-iodovinyl)benzene with ethyl diazoacetate.<sup>13</sup> A set of vinyldiazoacetates including unsubstituted, 3- and 4-substituted, as well as

3,4- and 4,4-disubstituted vinyl diazoacetates have been prepared to test the reaction scope. Under the optimized reaction conditions, the corresponding unsubstituted, 3-substituted and 3,4-disubstituted 1*H*-pyrazole-5-carboxylates have been obtained in yields of up to 95% (Schemes 4 and 5).

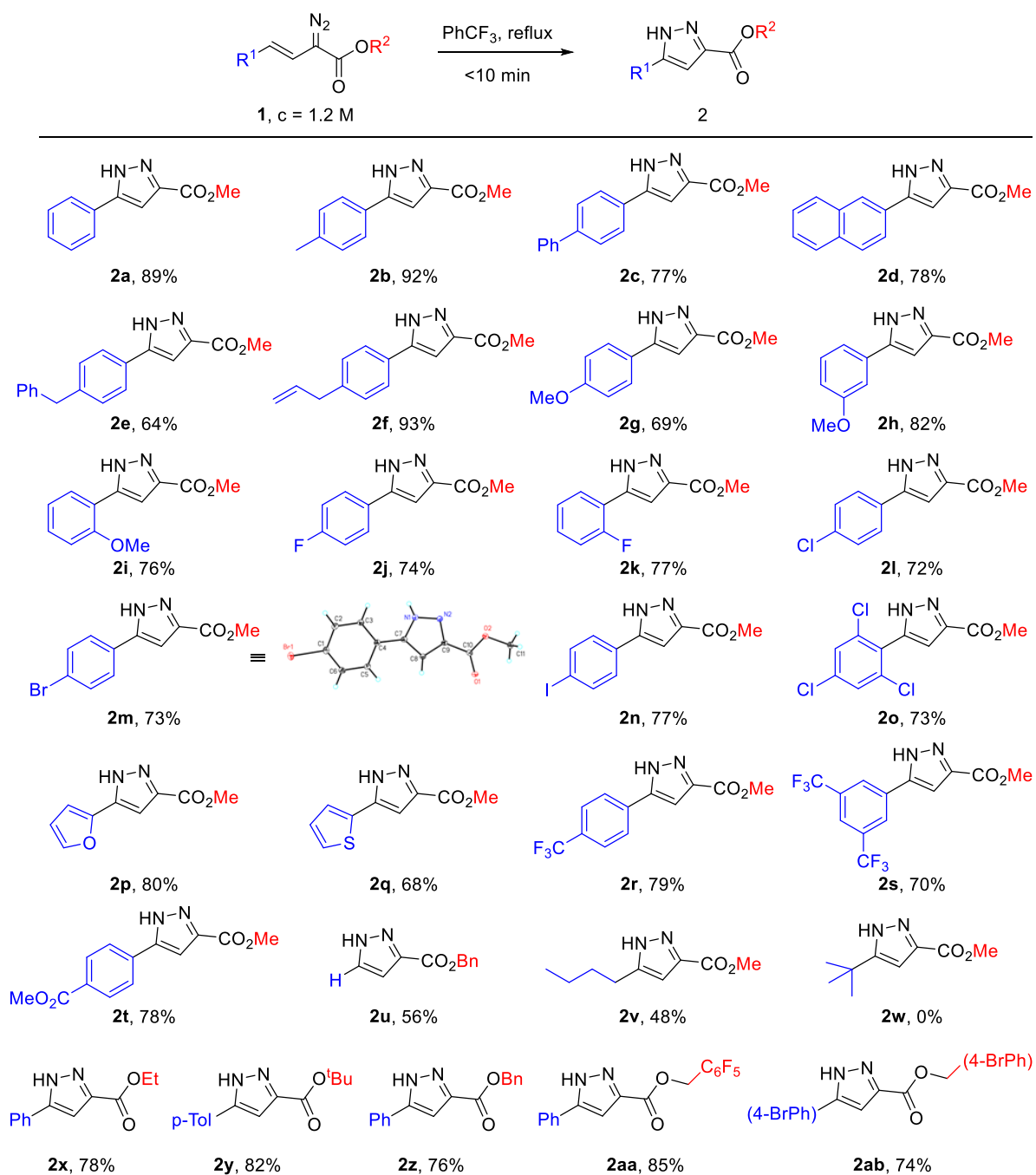


**Scheme 3** Structural conformation for products of diazotransfer to C2 of  $\beta,\gamma$ -unsaturated ester **1r**.

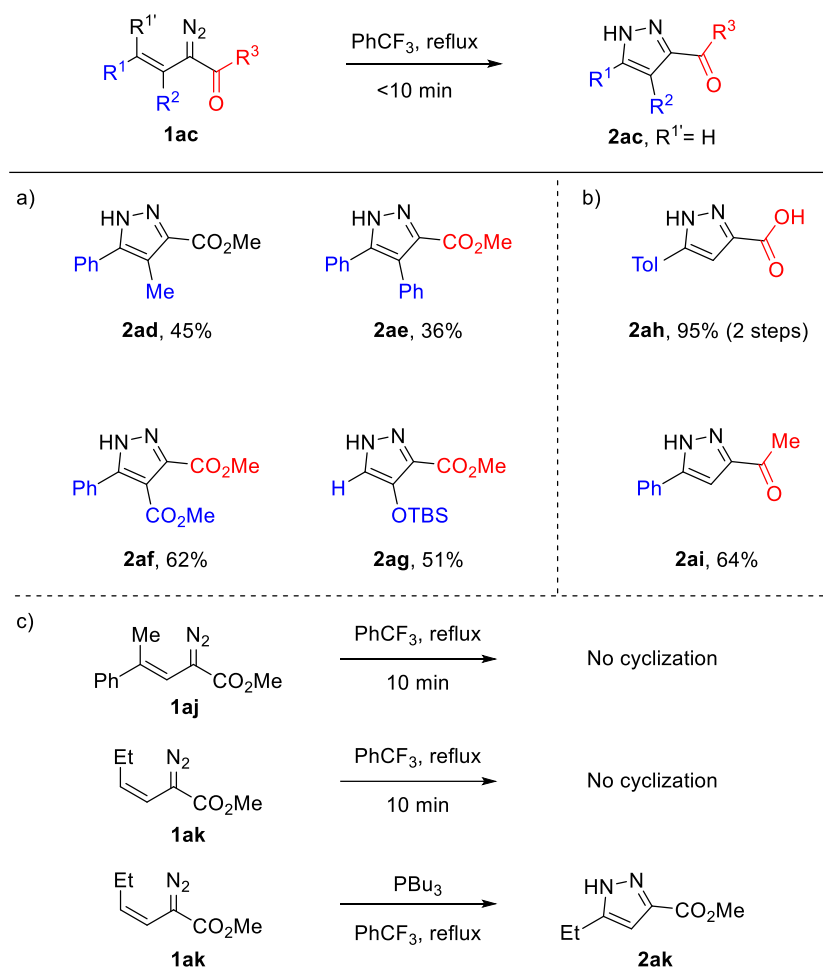
Differentially substituted aryl groups were installed at C4 of the vinyl diazoacetates in order to evaluate the electronic effects these substituents may have on the reaction outcome (Scheme 4). Vinyl diazoacetates carrying an electron rich aryl substituent in *ortho*, *meta* or *para* position resulted in good yields similar to those of the phenyl substituted diazo compound **1a** (**2a-2i**, yields 64-93%). Halogen-substituted aryl groups were well tolerated and the corresponding pyrazoles **2j-2o** suitable for further cross coupling could be obtained in 72-77% yield. The structure of product **2m** was unambiguously assigned by X-ray crystallography (Scheme 4). Pyrazoles carrying electron-deficient aryl substituent in C4 position were isolated in 70-79% yield (**2r-2t**) thus demonstrating that yields in these reactions are not strongly influenced by the electronic nature of the substituents. Furans and thiophenes were also well tolerated and the corresponding pyrazoles **2p** and **2q** were obtained in 80% and 68% yield, respectively. Alkyl substituents also allowed for the synthesis of pyrazoles albeit in lower yields owing to the lower stability of the diazoacetate and a more diverse network of the possible side reactions. When *n*-butyl group was present as the C4 substituent the corresponding pyrazoles **2v** was isolated in yield of 48%. When *t*-butyl-substituted vinyl diazoacetate was employed, the cyclization product could not be observed presumably due to the steric crowding at the reactive C4 carbon atom. Even the non-substituted vinyl diazoacetates underwent the cyclization to produce monosubstituted pyrazole **2u** in 56% yield. In addition to the methyl esters, a variety of other alkyl and aryl esters were tolerated, including the benzylic and bulky *t*-butyl esters with isolated yields of pyrazoles ranging from 74% to 85% (**2x-2ab**). After establishing the reaction scope for disubstituted pyrazoles, the focus was shifted to the synthesis of trisubstituted pyrazoles (Scheme 5a). Both alkyl and aryl groups can be introduced at C3 of the vinyl diazoacetate, although with slightly lower yields (Scheme 5a). Electron withdrawing groups like esters were also well tolerated (**2af**, 62%), as were electron donors such as silyl enol ether in **2ag** (51%).

Finally, we set to explore if vinyl diazo compounds featuring an electron withdrawing group other than a simple ester could be competent cyclization substrates that produce the corresponding pyrazoles. Attempts to accommodate a nitrile, diethylamide, fluoride, trifluoromethyl or acetate instead of the ester failed at various points in the synthesis and did not afford the desired pyrazoles. The ester however, could be substituted by a carboxylic acid as in **2ah** or a ketone as in **2ai** (Scheme 5b). In the synthesis of the methyl ketone substituted pyrazole, the diazotransfer reaction proved selective for the

allylic methylene over the  $\alpha$ -methyl group of the ketone and the corresponding diazo compound underwent efficient cyclization to the pyrazole **2ai** in 64% yield. The cyclization to form 1*H*-pyrazole-3-carboxylic acid **2ah** proceeded with high rates and prevented isolation of the vinyldiazoacetic acid during basic hydrolysis of the ester precursor. This indicated that diazotransfer and cyclization could be done as a one pot process in the presence of the base and excess diazotransfer reagent. Overall yields for the tested one-pot process were lower, presumably due to the limited choice of solvents that would enable high yields in both diazotransfer and cyclization processes.



**Scheme 4** Reactions scope for synthesis of disubstituted pyrazoles.



**Scheme 5** a) Synthesis of trisubstituted pyrazoles. b) Accommodating electron-withdrawing groups other than esters at C2. c) 4,4-disubstituted- and *Z*-vinylacetates do not readily undergo cyclization.

Cyclization attempts with 4,4-disubstituted vinylacetate **1ab** and the *Z*-configured vinyl diazoacetate **1ac** under optimized conditions did not afford any of the cyclized 3*H*- or 1*H*-pyrazole products (Scheme 5c). The *Z*-vinyl diazoacetate, however, did form the corresponding pyrazole in the presence of a Lewis base that promotes *Z/E* isomerization, like nucleophilic phosphines. Based on these experiments, it can be conjectured that the reactions likely proceed as thermal 6π electrocyclizations to 3*H*-pyrazoles followed by the 1,5-proton shift. We consider C-N bond cleavage an unlikely scenario as it would irreversibly produce dinitrogen. A simple crossover experiment where a mixture of two vinyl diazoacetates with different C4 and ester substituents were used in a 1:1 mixture, demonstrated that these reactions do not proceed via a dissociative pathway that would include C-C cleavage leaving a simple thermally induced electrocyclization as the most plausible mechanistic scenario.

In summary, thermal 6π electrocyclization of vinyl diazoacetates to 3*H*-pyrazoles followed by the 1,5-proton shift is an effective strategy for synthesis of trisubstituted 1*H*-pyrazoles with substituents on all three carbon atoms. The reactions are operationally simple, require no catalyst and proceed with high rates at elevated temperatures. Reaction scope is broad with both alkyl and aryl

substituents tolerated at positions 4 and 5 of the pyrazoles. An electron withdrawing group: an ester, a carboxylic acid or a ketone, is required in the vinyldiazo compound and is installed in position 3 of the pyrazole. The reactions proceed in good yields regardless of electronic properties of the substituents and afford a variety of pyrazoles that are of interest in different branches of chemical industry.

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### Graphical Abstract

