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The Aza–Markovnikov Reaction in the Pyrazole Series with Vinyl Trifluoroacetate

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Abstract

Vinyl trifluoroacetate reacts instantaneously with pyrazoles under catalyst-free conditions, sharply contrasting with the unreactive behavior of vinyl acetate. This unprecedented transformation proceeds via initial Markovnikov addition followed by a spontaneous secondary nucleophilic attack of the pyrazole ring, ultimately delivering functionalized aminals through a rare secondary C = C bond addition pathway. This operationally simple, multicenter process offers a direct entry into complex heterocyclic architectures. The structures of all synthesized compounds were rigorously established using IR, ^{1}H NMR, ^{13}C NMR, and mass spectrometry.

Introduction

Aza–Markovnikov reactions, akin to aza–Michael additions, represent one of the most direct and atom-economical approaches for C–N bond formation in organic synthesis [1–3]. The resulting nitrogen-containing heterocycles are vital structural motifs in medicinal chemistry and drug discovery, as they frequently exhibit a broad spectrum of biological activities. Among these, bis(azole)-containing frameworks are widely encountered in biologically active natural products and pharmaceuticals. For instance, streptindole alkaloids exhibit pronounced antimicrobial and cytotoxic activities, while arundine derivatives have attracted considerable interest for their diverse biological properties. Furthermore, bis(azole) architectures serve as potent receptor ligands and protein–protein interaction inhibitors [4]. Representative examples include PSB-16671, a selective P2Y1 receptor antagonist, and MDM2–p53 inhibitors, which hold significant promise in anticancer therapy by restoring p53 tumor suppressor activity. Additionally, the clinically established antifungal drug fluconazole features a bis(triazole) scaffold, functioning through the inhibition of fungal cytochrome P450-dependent lanosterol 14α-demethylase to block ergosterol biosynthesis [5]. These examples underscore the high pharmacological relevance of nitrogen-rich bis(azole) scaffolds. In contrast to aza–Michael additions [6], conventional aza–Markovnikov reactions typically lack efficiency in the absence of a catalyst. Over the years, various strategies have been developed to promote these transformations, ranging from phase-transfer catalysis to ionic liquid media [7–9].

In the early 2000s, synthetic methodologies for the aza–Markovnikov addition of azoles to vinyl esters were introduced using C-acylases as biocatalysts [10], followed by subsequent reports utilizing ionic liquids [9, 11, 12]. Despite their synthetic utility, these protocols often suffer from practical drawbacks, such as the requirement for excess amounts of vinyl esters and the use of hazardous solvents like DMF. While catalytic systems play a central role in modern organic synthesis, many conventional organocatalysts, enzymes, homogeneous metal complexes, and ionic liquids remain expensive or operationally demanding, creating a strong demand for more sustainable and streamlined methodologies. In this context, Kupai and co-workers demonstrated the use of Cinchona alkaloids as organocatalysts for aza–Markovnikov transformations [13].

Building upon these precedents and aiming to address existing limitations, our group previously reported aza–Markovnikov reactions promoted by transition metals immobilized on polyvinylazole supports [14]. Nevertheless, to the best of our knowledge, catalyst-free protocols for aza–Markovnikov reactions remain entirely absent from the literature. Herein, we report the first example of a catalyst-free aza–Markovnikov reaction of pyrazoles with vinyl trifluoroacetate under mild conditions, providing a direct, highly efficient route to bis(pyrazolyl) derivatives.

Results and Discussion

Literature precedence indicates that aza–Markovnikov additions of azoles to vinyl acetate and its conventional analogues typically require catalytic activation. Among these analogues, however, vinyl trifluoroacetate has remained largely unexplored. To our surprise, initial experiments involving pyrazoles 1–3 and vinyl trifluoroacetate revealed that the aza–Markovnikov reaction proceeds vigorously and instantaneously, even in the complete absence of any catalyst (Scheme 1).

To moderate the reaction, the reagents were pre-cooled to ca. −10°C, and the mixture was subsequently allowed to stir at room temperature (20–25°C) for 24 h. Unexpectedly, structural analysis of the isolated products revealed that, rather than the anticipated mono-adducts, bis(pyrazolyl) derivatives 4–6 were exclusively obtained (Scheme 2). Mechanistically, the transformation is initiated by the nucleophilic attack of pyrazoles 1–3 at the α-carbon of the vinyl moiety, generating the primary aza–Markovnikov intermediate. This reactive species then undergoes a rapid, spontaneous secondary nucleophilic attack by a second molecule of the pyrazole, culminating in the formation of the corresponding aminal architecture (Scheme 2).

The second stage of the transformation proceeds readily, consistent with the well-established fact that the CF_3COO group serves as an excellent leaving group [15, 16]. Methyl substituents on the pyrazole ring typically increase electron density at the pyridine-type nitrogen atom. Consequently, one might intuitively expect 3,5-dimethylpyrazole (pKa = 4.38) to afford higher yields compared to unsubstituted pyrazole (pKa = 2.53) and 3(5)-methylpyrazole (pKa = 3.55). However, the opposite trend was observed experimentally.This unexpected outcome is attributed to the in situ generation of trifluoroacetic acid during the second stage, which hinders further reaction progression. Specifically, under these acidic conditions, the more basic 3,5-dimethylpyrazole (3) undergoes rapid protonation, rendering it unreactive and leaving unreacted starting material in the mixture.Furthermore, reactions involving 3(5)-methylpyrazole inherently yield mixtures of N-substituted 3-methyl and 5-methyl isomers [17]. In accordance with ^{1}H NMR data, compound 5 similarly exists as a mixture of two regioisomers (3,3'-dimethyl and 3,5'-dimethyl), whereas the 5,5'-dimethyl isomer is completely absent, as unambiguously confirmed by NOESY spectral analysis (Scheme 3).

It was further observed that the distillation of compound 6 at 190°C / 1 mmHg triggers thermal fragmentation, accompanied by the elimination of 3,5-dimethylpyrazole. The resulting 1-vinyl-3,5-

dimethylpyrazole fragment subsequently undergoes rapid thermal polymerization under these conditions.

Analogous transformations have been reported in the synthesis of vinylpyrazoles [18]; however, those processes required elevated temperatures (250°C) and the presence of p-toluenesulfonic acid. To further demonstrate the synthetic utility of the developed methodology, its application toward the synthesis of Vibrindole A, a naturally occurring antibiotic, was investigated. Vibrindole A has attracted considerable interest owing to its potent biological activity and structurally distinctive nitrogen-containing heterocyclic framework. As illustrated in Scheme 5, the key catalyst-free aza–Markovnikov addition provided straightforward access to a crucial synthetic intermediate, which was subsequently elaborated into Vibrindole A in a concise and efficient manner. The successful preparation of this antibiotic underscores the practical value of the methodology beyond mere theoretical development, highlighting its strong potential for the synthesis of biologically active molecules. Ultimately, these results demonstrate that this catalyst-free transformation serves as a versatile and sustainable platform for the rapid construction of complex nitrogen-containing architectures relevant to medicinal and natural product chemistry.

Experimental Part

1,1'-(Ethane-1,1-diyl) bis(1H-pyrazole) (4)

A 50 mL tube was charged with pyrazole (1.0 g, 0.014 mol), previously cooled to − 10°C, and vinyl trifluoroacetate (3.0 g, 0.022 mol). After charging, the tube was immediately closed and mixed under 20–25°C condition for 24 h. Then the tube was opened, and the reaction mixture was neutralized with an aqueous solution of Na_2CO_3 to pH = 8. The mixture was extracted with dichloromethane, and the organic layer was dried over anhydrous Na_2SO_4. After standing overnight, the drying agent was removed by filtration, and the solvent was evaporated under reduced pressure. The resulting residue was purified by column chromatography with EtOAc/Hexane system. Compound **4** was obtained as 0.95 g (79.4%) of a white crystal, mp 48–49°C.

1,1'-(Ethane-1,1-diyl) bis(3(5)-methyl-1H-pyrazole) (5a, b)

Following the procedure described above, the reaction of 3(5)-methylpyrazole (1.0 g, 0.012 mol) with vinyl trifluoroacetate (2.5 g, 0.018 mol) afforded compounds **5a** and **5b** as a mixture (0.69 g, 60.8% yield). The product was obtained as a colorless liquid; b.p. 110–112°C (1 mmHg), n_D^{25} = 1.4925.

1,1'-(Ethane-1,1-diyl) bis(3,5-dimethyl-1H-pyrazole) (6)

Compound **6** was obtained following the procedure described above from 3,5-dimethylpyrazole (1.0 g, 0.010 mol) and vinyl trifluoroacetate (2.1 g, 0.015 mol). After removal of the solvent, an oily residue was

obtained, which was dissolved in 20 mL of a hexane/diethyl ether solvent mixture (3:1, v/v) and kept at −15°C for 24 h. The resulting crystals were separated and identified as unreacted 3,5-dimethylpyrazole and were discarded. The hexane–diethyl ether solvent was then removed, affording crystalline material with a melting point of 80–85°C. According to NMR analysis, the isolated product corresponds to compound **6**. The yield was approximately 40% (0.45 g). IR, ^{1}H NMR, ^{13}C NMR, and mass spectrometry data are provided in the Supporting information

3,3'-(Ethane-1,1-diyl)bis(1H-indole) – Vibrindole A

Yellow solid with 59% isolated yield (Rf = 0.3, EtOAc/Hexane 1:3). (4.7 mmol scale, 721 mg), ¹H NMR (400 MHz, CDCl3): 7.87 (d, 1.4H), 7.79 (d, 0.6H), 7.77 (d, 1.2H), 7.65 (d, 0.8H), 7.45–7.42 (m, 1.3H), 7.38–7.32 (m, 1.4H), 7.28–7.19 (m, 3.3H), 7.0 (dd, 0.7H), 6.96 (dd, 0.3H), 6.64 (d, 0.7H), 4.84 (q, 0.3H), 4.69 (q, 0.7H), 1.99–1.95 (d, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): 136.73, 127, 121.85, 121.69, 121.36, 119.82, 119.1, 111.22, 28.27, 21.85 ppm. HRMS (ESI, m/z) calcd. for $C_{18}H_{16}N_2$ $[M + H]^+$: 261.1313, found: 261.1308.

Declarations

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Consent to Publish declaration: Not applicable.

Ethics and Consent to Participate declarations: Not applicable.

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Author Contribution

A.A. conducted the main investigation and synthesis together with A.S. L.K. performed mechanistic studies. H.N. prepared the original manuscript draft. H.A. contributed to the synthesis and mechanistic investigations. R.H. and H.A. supervised the research and provided guidance throughout the project. All authors reviewed and approved the final manuscript.

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Schemes

Schemes 1 to 5 are available in the Supplementary Files section

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