SIMULTANEOUS DENITRATIVE C–C BOND FORMATION AND CONSTRUCTION OF PYRAZOLE RING LEADING TO 1,1'-DIPHENYL-4,4'-BIPYRAZOLE

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Abstract – β-Formyl-β-nitroenamine reacts with phenylhydrazine to afford 1,1'-diphenyl-4,4'-bipyrazole. The unusual C–C bond formation was found to proceed in an ionic mechanism initiated by excess amount of hydrazine. This reaction is interesting from a viewpoint of synthetic chemistry because it simultaneously involves the construction of a pyrazole ring and the formation of a C–C bond under neutral conditions.

β-Formyl-β-nitroenamine (1) possesses multiple functionalities such as α,β-unsaturated aldehyde, nitroalkene, and enamine. The push–pull property generates a highly electron-biased C–C double bond, which reacts with either nucleophiles or electrophiles to afford versatile heterocyclic frameworks (Scheme 1).1 When nitroenamine (1) was reacted with dinucleophilic reagents such as hydrazines (2), amidines, 1,2-diamines, and ketones, the corresponding nitrated pyrazoles (3), pyrimidines, 1,4-diazepines, and phenols were formed, respectively.1,2 In these reactions, 1 serves as a safely handleable synthetic equivalent of unstable nitromalonaldehyde (NMA).3

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Scheme 1. Versatile reactivities of nitroenamine (1)
While nitroenamine (1) efficiently reacts with aliphatic hydrazine at room temperature, reactions with aromatic hydrazines require heated conditions to afford the corresponding nitropyrazoles; however, the yields are moderate, which prompted us to study the latter reaction in detail. When an ethanol solution of nitroenamine (1) and an equimolar amount of phenylhydrazine (2a) at 90 °C for 1 d, 1-phenyl-4-nitropyrazole (3a) was obtained in 65% yield together with several unidentified by-products. Although using 2 equiv. amounts of 2a afforded a simple reaction mixture, using larger amounts of 2a (4 equiv.) only furnished similar result. From the reaction mixture, two products were isolated by column chromatography, of which nitropyrazole (3a) was the major product (54% yield). The 1H NMR spectrum of another product revealed same signal pattern as 3a (1,4-disubstituted pyrazole), but the mass spectrum indicated that it is a dimeric product, hence, the product was determined as 1,1'-diphenyl-4,4'-bipyrazole (4a) (41% yield) (Scheme 2). Several other reaction conditions; however, yields of 4a did not increase further. When 4-nitrophenylhydrazine (2b) was used instead of 2a, formation of nitropyrazole (3b) was confirmed, but the reaction mixture was somewhat complicated, and bipyrazole (4b) was not detected, which was presumably due to the less nucleophilicity of 2b.

Bipyrazoles are often found in biological active compounds and used as a ligand constructing MOF. Accordingly, numerous synthetic methods have been reported. The main methods include transition-metal-catalyzed coupling reaction and halogenating reagent-promoted coupling reaction of pyrazoles, or construction of pyrazole rings using polyfunctionalized substrate. To the contrary, the present reaction includes a construction of pyrazole ring and a coupling reaction accompanied by denitrative C–C bond formation under neutral conditions, which is a hitherto unknown reaction type. Isolated nitropyrazole (3a) caused no change upon treatment with phenylhydrazine (2a) under the same conditions, hence, bipyrazole (4a) was formed through different reaction path. When the reaction 1 and 2a was conducted in the presence of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO), no suppression was observed to afford products (3a) and (4a) in 44% and 43% yields, respectively, which indicates that this reaction proceeds through ionic mechanism.
Based on the experimental results, one of the plausible mechanisms for formation of 3a is illustrated in Scheme 3. The reaction is initiated with the reaction of 2a at the formyl group of 1 to form hydrazone (5). With aliphatic hydrazines, the alkylamino moiety is sufficiently nucleophilic to efficiently construct a
pyrazole ring at room temperature. In contrast, the phenylamino moiety of aromatic hydrazone (5) is less nucleophilic and requires heated conditions to construct a five-membered ring (path a), followed by aromatization with elimination of tert-butylamine to yield nitropyrazole (3a) (path b). Hence, the slow formation of the pyrazole ring from 5 is considered to undergo the competitive dimerization. The fact that isolated pyrazole (3a) was treated under the same conditions and recovered without any change suggests that the dimerization occurred via different reaction paths in the intermediate stage before aromatization. Denitrative dimerization of nitroalkenes is hitherto unknown to the best of our knowledge, and thus it is necessary to produce nitroalkanes as plausible intermediates. Since an equimolar amount of 2a does not give bipyrazole (4a), another molecule of hydrazine (2a) for homo-coupling, which destroying the conjugate system to give nitroalkane. Several possible intermediates can be considered, among which two intermediates (7) and (8) are illustrated in Scheme 3. Instead of slow ring closure (path a), a competitive attack from another hydrazine (2a) to the imino group occurs, yielding nitroalkane (7) (path c). Pyrazolidine (8) obtained from intermediate (6) is also an acceptable intermediate for homo-coupling (path d). As another possibility, a reaction path initiated by attack of hydrazine (2a) at the β-position of a nitro group of 1 including formation of an aminal and bis(hydrazone) can be considered. Dimerization of nitroalkanes represented by Nef-type reaction is commonly used in organic synthesis; however, the use of strong bases and halogenating reagent is often used to facilitate the reaction. On the contrary, neither strong base nor halogenating reagents are required for this reaction. In other words, nitronic acid appears to be the actual active species in this homo-coupling (Scheme 4). Nitroalkanes (7) or (8) tautomerize to nitronic acid (8), forming a C–C bond to afford dimeric product (9) (Scheme 4). Nitroamine, nitrosamine, and hydrazine are thought to eliminate more readily than that of nitrous acid or amine to release the strain by steric repulsion of amino and nitro groups, yielding bipyrazole (4a).

In summary, a novel synthetic route to bipyrazole was found, in which construction of a pyrazole ring and denitrative C–C bond formation simultaneously occurred. Since this method requires neither harsh reaction conditions nor special reagents, insights obtained here will provide useful information in nitro and pyrazole chemistry.

**EXPERIMENTAL**

**General**

All reagents and dry solvents were purchased from commercial sources and used as received. \(^1\)H and \(^{13}\)C\{\(^1\)H\}\) spectra were recorded on JEOL JMN-ECZ400S spectrometer (400 MHz and 100 MHz, respectively) in a deuterated chloroform using TMS as an internal standard. The assignments of the
\(^{13}\text{C}\{^{1}\text{H}\}\) NMR were performed by DEPT experiments. High-resolution mass spectra were obtained on an AB SCEIX Triplet TOF 4600 mass spectrometer.

**Reaction of nitroenamine (1) and phenylhydrazine (2a)**

To a solution of nitroenamine (1) (35.3 mg, 0.2 mmol) in EtOH (3 mL), phenylhydrazine (2a) (40 µL, 0.4 mmol) was added, and the resultant mixture was heated at 90 °C in a sealed tube for 1 d. After removal of the solvent under reduced pressure, the residue was submitted to column chromatography on silica gel using hexane/EtOAc (9/1) to afford nitropyrazole (3a) (20.8 mg, 0.11 mmol, 54%) and bipyrazole (4a) (11.8 mg, 0.041 mmol, 41%) as orange solid, respectively. 1,1'-Diphenyl-4,4'-bipyrazole (4a): Orange solid.

\(^{1}\text{H}\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.30 (t, \(J = 7.2\) Hz, 2H), 7.48 (dd, \(J = 7.2, 8.8\) Hz, 4H), 7.72 (d, \(J = 8.8\) Hz, 4H), 7.88 (s, 2H), 8.08 (s, 2H); \(^{13}\text{C}\) NMR (100 MHz, CDCl\(_3\)) \(\delta\) 115.6 (C), 119.1 (CH), 123.3 (CH), 126.7 (CH), 129.6 (CH), 139.1 (CH), 140.2 (C); HRMS (ESI/TOF) calcd. for (M+H\(^+\)) \(\text{C}_{18}\text{H}_{15}\text{N}_{4}\): 287.1291, found: 287.1295.

**REFERENCES**


