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Divergent Construction of Pyrazoles via Michael Addition of *N*-Arylhydrazones to 1,2-Diaza-1,3-dienes

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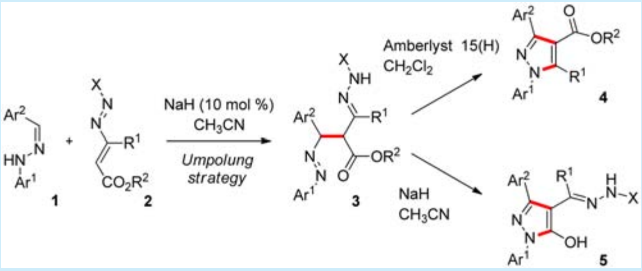
Supporting Information

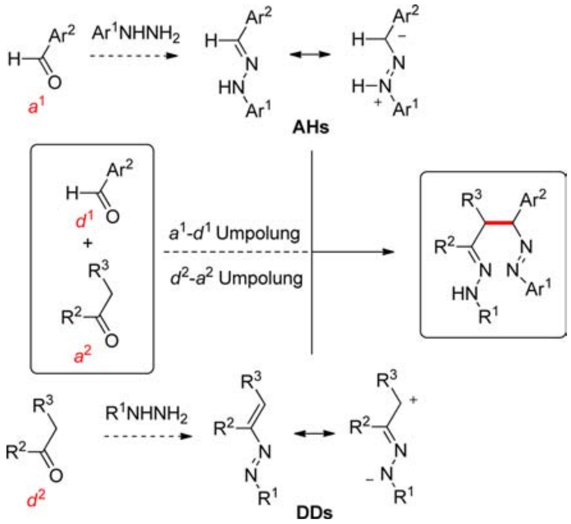
ABSTRACT: The base (NaH)-promoted Michael addition of *N*-arylhydrazones (AHs) with 1,2-diaza-1,3-dienes (DDs) produces unprecedented *β*-azohydrazone adducts. Strategically, the use of AHs as acyl anion equivalents (d^1 synthon) and DDs as *α*-electrophiles (a^2 synthon) of carbonyl compounds open the way to two important classes of pyrazole compounds.



The de novo construction of complex structures by use of umpolung strategies represents an exciting area of study in organic synthesis. In this regard, the umpolung[1] concept, introduced by Corey and Seebach, has been applied to unconventional molecular assembly, providing flexibility, chemoselectivity, and efficiency in the synthesis of biologically active target molecules.[2,3] Whereas the natural reactivity of an aldehyde (a^1 reactivity) requires a reaction with a ketone enolate (d^2 reactivity) and leads to the aldol addition product,[4] we envisioned a conjugated addition in which a formal umpolung of both reagents occurs (Scheme 1). For this purpose, the transformation of a carbonyl group into a hydrazone functionality (as masked carbonyl of aldehydes or ketones) is one valuable tactic. It is well-known that hydrazones and their derivatives can be employed as attractive system of both acyl anion equivalents (i.e., arylhydrazones) and *α*-electrophiles (i.e., 1,2-diaza-1,3-dienes).

The chemistry of arylhydrazones[5] (AHs) and 1,2-diaza-1,3-dienes[6] (DDs) has been under study for a long time in various fields ranging from organic chemistry to supramolecular chemistry. Based on the multifaceted behavior of these reagents and given our interest in the search of new strategies for the construction of azaheterocycles, we became interested in probing the reactivity of AHs with DDs. In a beautiful paper, Glorius and co-workers developed intriguing NHC-catalytic switchable reactions of enals with azoene to generate diazepines and pyrazoles.[6c] To date, this work represents the sole example of an umpolung reaction involving an azoene compound as Michael acceptor. On the other hand, very few synthetic strategies using the azaenamine character of monosubstituted hydrazones has been exploited for the functionalization of electrophiles (i.e., acrylate, acrylonitrile, *α*,*β*-unsaturated aldehydes/ketones, nitroalkenes, *α*-keto esters, aldehydes) leading to synthetically useful diazene compounds.[7] Despite the importance of N═N bonds, the preparation of diazenes containing the versatile hydrazone group still remains challenging. Through polarity reversal, or "umpolung", we show here that ketone and aldehyde hydrazones can be used as versatile precursors for the divergent assembly of pyrazole structures after the conjugated addition to *β*-azohydrazone compounds takes place. Specifically, DD serves as an a^2 synthon, which formally installs an d^1 synthon onto the original *α*-carbon of an carbonyl compound, thus providing a conceptually new way to form C−C bond. (Scheme 1)

Scheme 1. Umpolung of the Reactivity of Carbonyl Compounds: Michael Addition Reaction of AHs with DDs



Our investigations focused on the conjugate addition of AH **1a** to DD **2a**. Initially, we conducted the reaction in CH_3CN at

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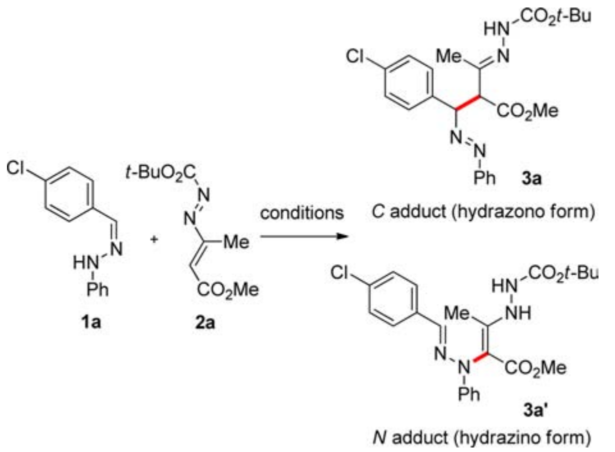
room temperature in the absence of any catalyst as a background reaction. As a result, the TLC check revealed no formation of products (Table 1, entry 1). Different solvents, for example CH_3CN, Et_2O, CH_2Cl_2, CH_3OH, and *t*-BuOH, in the presence of various commonly and inexpensive acid and basic catalysts were tested. Interestingly, when acidic conditions were used, only corresponding N-adduct **3a′** (hydrazino form) was recovered (Table 1, entries 2−6). Similar results were also obtained by using bases such as Na_2CO_3 or CH_3ONa (Table 1, entries 8 and 9). When the reaction was conducted in the presence of DIPEA, not only the N adduct **3a′** was formed in 20% yield but the C-adduct **3a** was also obtained in 25% yield (Table 1, entry 7). To our delight, the exposure of **1a** and **2a** to NaH led to the exclusive formation of the C-adduct **3a** in excellent yields (83%) (Table 1, entry 11). The use of strong base as *t*-BuOK or decreasing the reaction temperature to 0 °C resulted in no increase in yield (Table 1, entries 10 and 12). These results mirror the observations made by Deng and Mani on reactions of *N*-monosubstituted hydrazones with nitroalkenes, who highlighted that the site selectivity (*C* versus *N*) is strongly dependent on the reaction conditions.[7g,8]

Table 1. *C* versus *N* Selectivity in Reaction of AH 1a with DD 2a[a]

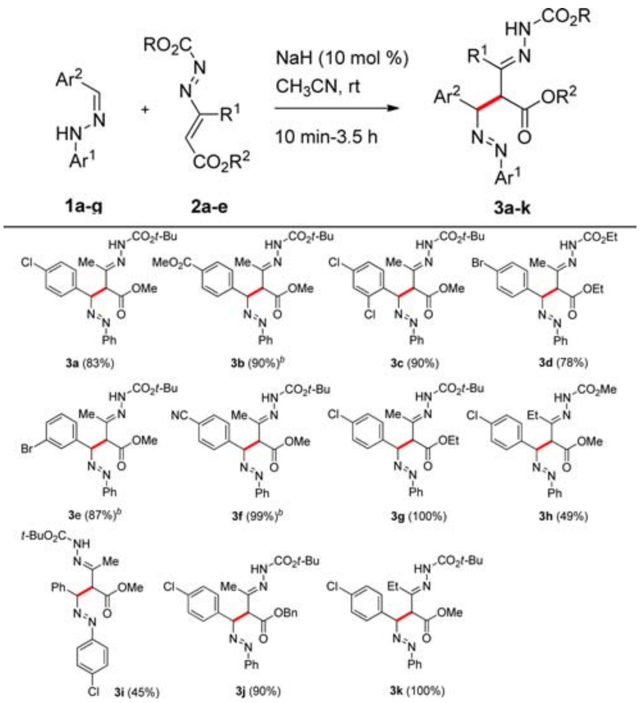


entry	catalyst (mol %)	solvent	temp (°C)	3a yield[b] (%)	3a′ yield[b] (%)
1		CH_3CN	rt		
2	TFA (20)	CH_3CN	rt		39
3	TFA (20)	CH_3OH	rt		77
4	TFA (20)	Et_2O	rt		37
5	Amberlyst 15(H)	CH_3CN	rt		41
6	$ZnCl_2$ (20)	CH_3CN	rt		86
7	DIPEA (10)	CH_2Cl_2	rt	25	20
8	Na_2CO_3 (10)	CH_2Cl_2	rt		27
9	CH_3ONa (10)	CH_3OH	rt		47
10	*t*-BuOK (10)	*t*-BuOH	rt	18[c]	
11	NaH (10)	CH_3CN	rt	83	
12	NaH (10)	CH_3CN	0	70	

[a]All reactions were performed at a 0.8 mmol scale **1a** using 1.1 equiv or 1.5 equiv of DD **2a** upon acidic or basic catalysis, respectively. [b]Yields of isolated product. [c]Starting **1a** (45%) was also recovered.

With these optimized reaction conditions in hand, the substrate scope with respect to both hydrazones[9] and DDs[10] was then investigated in order to evaluate the performance of this *C*-selective Michael addition reaction. As summarized in Scheme 2, different AHs **1a−g** and DDs **2a−e** were found to be tolerant of the reaction, providing the corresponding *β*-azohydrazone adducts **3a−k**.[11] Either electron-neutral (H) and electron-withdrawing (3-Br, 4-Br, 4-Cl, 4-CN, 4-CO_2Me, 2,4-Cl_2) substituents on Ar^1 and Ar^2 groups are well tolerated (Scheme 2, 45−100%). Also, a variety of azoene partners having different substituents (R, R^1, R^2 = Me, Et, *t*-Bu, Bn) worked well to give the corresponding carba-Michael adducts.

Scheme 2. NaH-Promoted Conjugated Addition of AHs 1a−g to DDs 2a−e[a]



[a]Yield of pure isolated products. [b]Reaction performed at 0 °C.

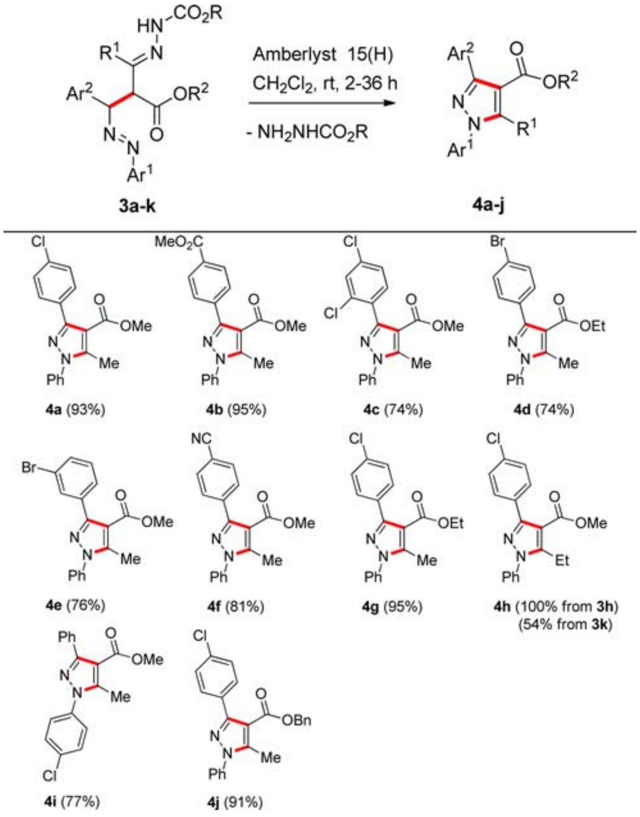
During the course of our study, we observed that upon exposure to $CDCl_3$, *β*-azohydrazone **3a** quickly disappeared along with a concurrent appearance of a new set of ^1H NMR signals, easily assignable to pyrazole structure **4a**. We also found that when the Michael reaction between AH **1a** and DD **2a** was conducted in the presence of a stoichiometric amount of NaH, a 32% of pyrazole **5a** along with the expected Michael adduct **3a** was isolated. Besides, direct conversion to pyrazole **4** was registered when 4-(*N*,*N*′-dimethylamino)carbonyl-DD ($CONMe_2$ instead of CO_2R^2) was used as azoene substrate upon exposure to catalytic amount of NaH. These findings prompted us to consider suitable reaction conditions to ensure the selectivity in the ring closure processes.

Thus, *β*-azohydrazones **3a−k** were successfully converted to pyrazoles **4a−j** by means of a simple acid (Amberlyst 15(H)) catalyzed cyclization (54−100%) (Scheme 3).

Then, we examined the ability of NaH to promote the formation of pyrazoles **5a−h** (33−76%) (Scheme 4).

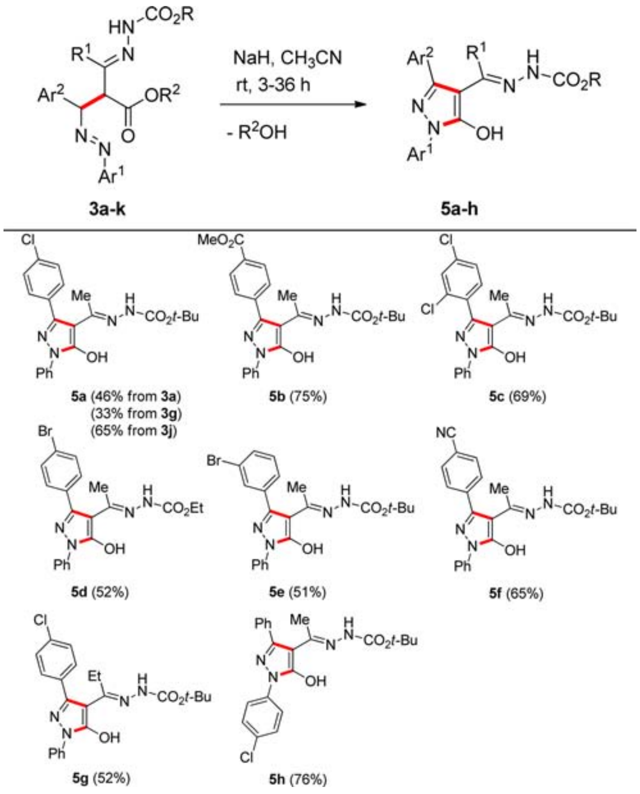
On the basis of the results obtained, a plausible mechanism for the divergent synthesis of pyrazoles **4** and **5** is proposed (Scheme 5). Assuming a stepwise pathway, deprotonated hydrazone **I′** would be responsible for the initial regioselective C attack at the terminal carbon of the DD **2** to furnish *β*-azohydrazone intermediate **3**. Two different 5-*exo-trig* cyclizations would then occur. When acidic conditions are used a

Scheme 3. Cyclization of Adducts 3a−k to Pyrazoles 4a−j[a]



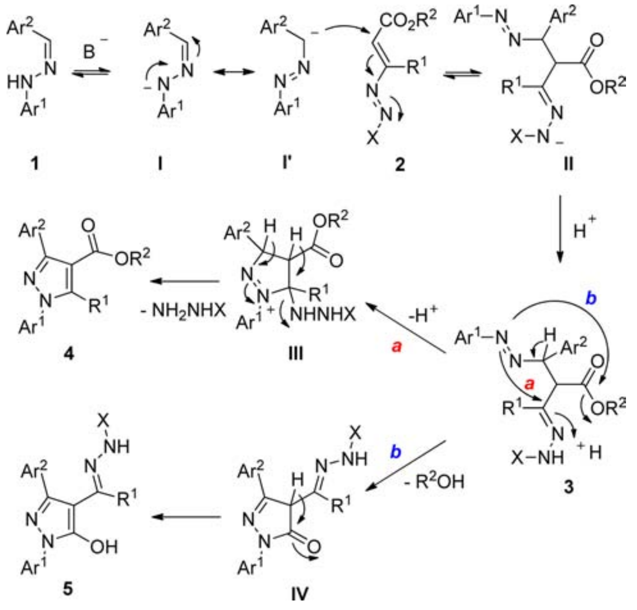
[a] Yield of pure isolated products.

Scheme 4. Cyclization of Adducts 3a−k to Pyrazoles 5a−h[a]



[a] Yield of pure isolated products.

Scheme 5. Plausible Mechanism



nucleophilic attack of the Ar^{1}N nitrogen atom onto the activated C═N function would lead to pentacyclic intermediate **III**, which could produce pyrazole **4** by loss of the hydrazine residue and 1,3-H shift reaction (Scheme 3, path a).[12] On the other hand, NaH-mediated cyclization to pyrazole **5** would occur from intermediate **3** via preliminary 1,3-H shift followed by intramolecolar nucleophilic attack of the Ar^{1}N nitrogen atom on a ester function (intermediate **IV**) and alcohol elimination (Scheme 3, path b). It is important to note that the presence of an ester group (CO_2R^2 instead of the amide group $CONMe_2$) is essential to ensure this cyclization path, presumably due to its greater ability as leaving group.

The pyrazole ring system found in products **4** and **5** is a heterocyclic core amenable to application in medicinal, pesticide, and coordination chemistry. For example, *N*-aryl-functionalized pyrazoles of type **4** are known to have diverse biological activities, such as HIV protease inhibitors and anti-inflammatory, antiobesity, analgesic, antidiabetic and antitumor agents.[13] A number of commercial drugs and pesticides such as Celebrex, Eliquis, Acomplia, and Fipronil have been successfully commercialized. In addition, 5-hydroxy-4-acylpyrazole hydrazones such as **5** are of interest as effective chelating/extracting reagents for many metal ions and photochromic materials.[14] In view of the importance of these target molecules, we hope this methodology may be of value for future applications.

In summary, we found that AHs **1** can react with DDs **2** in the presence of NaH as a promoter. In this way, an intriguing β-azohydrazone intermediate was obtained formally, inverting the usual reactivity of carbonyl compounds (aldehyde and ketones). The carbo-Michael adduct so prepared was shown to be the key intermediate for subsequent chemoselective cyclizations to functionalized pyrazole compounds. Further studies are presently in progress in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(9) AHs **1a**–**g** were synthesized via condensation reaction from aldehydes and hydrazines (see the Supporting Information).

(10) DDs **2a**–**f** were synthesized from the corresponding halohydrazones by treatment with base (see the Supporting Information).

(11) Compounds **3a**–**k** exhibit a pronounced tendency to undergo isomerization and/or partial decomposition when exposed to DMSO-d_6 solution; for these reasons, all attempts to obtain their fully characterization were unsuccessful.

(12) An alternative pathway in which CH/NH tautomerization may precede the cyclization step should be excluded according to our previous findings. See: Attanasi, O. A.; Filippone, P.; Fiorucci, C.; Mantellini, F. *Tetrahedron Lett.* **1999**, *40*, 3891.

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