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Methyl Hydrazinocarboxylate as a Practical Alternative to Hydrazine in the Wolff–Kishner Reaction

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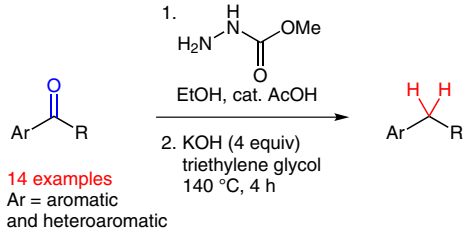
Dedicated to Professor Steven V. Ley on the occasion of his 70th birthday.



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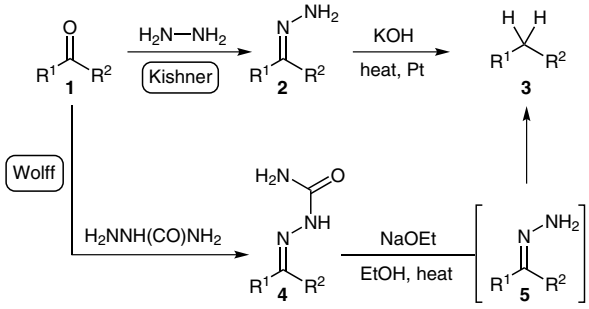
Abstract Herein we describe a facile protocol for the reduction of aromatic ketones and aldehydes to the corresponding methylene unit. The procedure involves isolation of a carbomethoxyhydrazone intermediate that is easily decomposed to the reduced product without the requirement for large quantities of pernicious hydrazine.

Key words reduction, aldehydes, ketones, heterocycles, hydrazones, alkanes

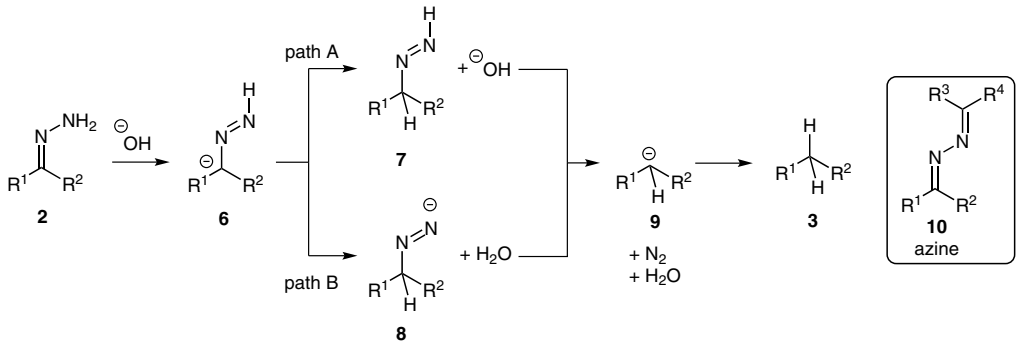


Scheme 1 The Wolff and Kishner reductions of aldehydes and ketones to the corresponding hydrocarbon

Since its independent discovery by Kishner (1911)[2] and Wolff (1912)[3] the eponymous reduction has become a standard method for the deoxygenation of aldehydes, ketones, and, for certain substrates, the carbonyl of amides under basic conditions.[4] However, the early investigations of Staudinger (1911) should not be forgotten.[5] In detail, they are two reactions proceeding through a common intermediate. The original procedure reported by Kishner involved prior generation of a hydrazone from the carbonyl and 100% hydrazine hydrate with subsequent base-catalysed decomposition over hot, solid KOH and platinised porous plate to deliver the corresponding hydrocarbon. Conversely, the Wolff version proceeded via an intermediate semicarbazone to decomposition over NaOEt in EtOH in a sealed tube around 180 °C (Scheme 1).

Since these initial disclosures, several modifications to the original procedures have been developed but, in general, those modifying the Kishner procedure have found the widest use. Perhaps the practically most significant development was introduced by Huang-Minlon.[6] Refining work by Soffer et al.[7] and Whitmore et al.,[8] this procedure took advantage of a high-boiling solvent such as diethylene or triethylene glycol and used potassium or sodium hydroxide as base with a distillation protocol to reduce water and hydrazine levels, permitting higher temperatures in the reaction pot. Recently, Kuethe et al. have adapted this protocol to the kilogram scale.[9] Nagata and Itazaki proposed a variant based upon use of an excess of the safer 85% hydrazine hydrate in the presence of a lesser quantity of its HCl salt, followed by heating in triethylene glycol and KOH.[10]

Attempts to lower the reaction temperature have been reported, initially by the Cram group; they reported reactions at room temperature using KO*t*-Bu in DMSO on the isolated hydrazone.[11] The effectiveness of this protocol has been interpreted by Szmant to result from the slow addition of the hydrazone, with consequent excess of base, and one equivalent of *t*-BuOH trapped within the solvent cage.[12] Henbest favoured refluxing toluene with a KO*t*-Bu base; again with the ability to generate the hydrazone anion with a molecule of *t*-BuOH within the solvent cage.[13] More recently, Myers has developed a highly effective reaction that begins with 1,2-bis(*tert*-butyldimethylsilyl)hydrazine, allowing silylhydrazone formation under Lewis acid mediated conditions, prior to base-mediated conversion into the



Scheme 2 Proposed mechanism for the Wolff–Kishner reaction[24]

hydrocarbon with KO*t*-Bu between 23 °C and 100 °C.[14] The Myers method also facilitates good yields in the Barton variation that allows for the preparation of vinyl iodides.[15]

Although less common, variations based upon the Wolff procedure have been described. For volatile products, Linstead reported that distillation from KOH removes the need for pressure vessels[16] and Quast et al. noted superior results for the decomposition of a semicarbazone, as compared to a Huang-Minlon protocol utilising hydrazine.[17] Interestingly, the substrate involved contains a 2-pyridyl subunit; a structural feature Szmant identified as promoting high reactivity.[18] Zengin also reports high yields of reductions from semicarbazones.[19]

Following early studies that explored Kishner's platinum/base reagents,[20] and the effect of different bases,[21] the mechanism of the solution-based Wolff–Kishner reduction was extensively studied by Szmant who determined the rate-limiting step to be C-protonation of the hydrazone anion **6** to give **8** (Scheme 2).[22,23] In a recent theoretical study, Yamabe identifies imine **7** as the intermediate formed during this protonation rather than the anion **8** favoured by Szmant.[24] Yamabe also identified a mechanistic distinction between substrates such as acetophenone, which give rise to a resonance-stabilised carbanion (with initial protonation occurring in the aromatic ring), and those such as acetone for which the final protonation is concerted, with no carbanion having an independent existence. The competition experiment reported by Taber, in which a Wolff–Kishner reaction was accompanied by a small fraction (ca. 5%) of stereoselective cyclisation onto a tethered alkene, supported the intermediacy of at least a proportion of sp^3 carbanion.[25]

Amongst the various substrates for the Wolf–Kishner reaction, those that might arise from a Friedel–Crafts reaction have a particular value as their reduction facilitates the classical approach for circumventing the overalkylation common in the corresponding alkylation reactions. It has been noted that substrates such as these, that give rise to relatively stable carbanion intermediates, generally give faster rates of reduction than those lacking that stability.[23] Additionally, this fast rate of reduction gives less opportunity for azine formation. Because of the very significant toxicity of hydrazine, it would be desirable to employ the Wolff version of this reduction and in some cases this has indeed proved to very successful, occasionally being superior to the classical Huang-Minlon procedure.[16,17] In our hands, decomposing the semicarbazone of acetophenone with KOH in triethylene glycol gave a moderate yield of ethylbenzene. We speculated that the initial cleavage of the semicarbazone, to afford the corresponding hydrazone, occurred via a β-elimination reaction. Taking into account the recent work of Beauchemin,[26] in which facile elimination occurs from a carboalkoxyhydrazone to afford an intermediate amino isocyanate, we concluded that treatment of a carbomethoxyhydrazone, under Huang-Minlon conditions, would afford good yields of the reduced product.

To this end, condensation of acetophenone and methyl hydrazinocarboxylate provided the carbomethoxyhydrazone intermediate (**13**) as a crystalline solid in excellent yield. In all cases, formation of the hydrazone intermediate was achieved by condensation of the parent carbonyl with methyl hydrazinocarboxylate (1.3 equiv) in ethanol with an acetic acid catalyst. The intermediates were bench-stable solids, and in all cases could be isolated by either filtration or flash column chromatography.

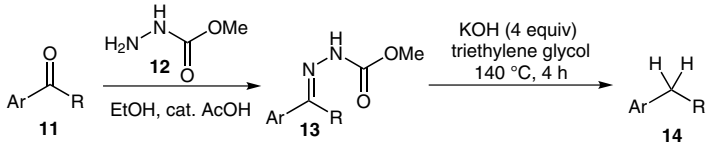
After extensive investigation, the optimal conditions for decomposition of this intermediate were found to be KOH in triethylene glycol at 140 °C. When using four equivalents KOH, the reaction was usually complete within four hours. If a faster rate was required, the number of equivalents of KOH could be increased with little effect on yield. It was noticed the predissolution of the KOH in the solvent was necessary before addition of the carbomethoxyhydrazone for optimal yield and reaction rate.

The reductions were performed on at least a 0.5 gram scale and in one case, (Table 1, entry 1) up to 8 grams of starting hydrazone could be used, with no change to the protocol, although upon initial addition of the substrate

some effervescence was observed. Substituted acetophenones and diaryl ketones were successfully reduced, as were a range of aromatic aldehydes.

Where the substrate was hindered (Table 1, entry 3) the yield was diminished and there was significant azine formation. Interestingly, *ortho*-anisaldehyde (Table 1, entry 6), despite the *ortho* substitution, resulted in a quantitative yield. Conversely, reduction of the 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde hydrazone derivative resulted in the azine product in 76% yield (see the Supporting Information for details). Bromo and chloro substituents were tolerated (Table 1, entries 2 and 4); however, the *p*-fluoro derivative underwent both reduction and S_NAr with the triethylene glycol solvent (see the Supporting Information for details). Heteroaromatic systems were also successfully reduced (Table 1, entries 10–13), but the volatility of some of the products resulted in some diminished yields. The reduction of aliphatic systems was attempted, but this was unsuccessful. In the case of camphor, a range of products were observed, most significantly the azine. Attempts to mitigate this included slow addition of the hydrazone to the basic mixture and increased dilution, but these were both unsuccessful; we attribute this to the instability of the proposed intermediate anion vide supra.[23]

Table 1 Synthesis of Reduced Aryl Species



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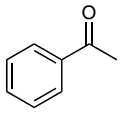
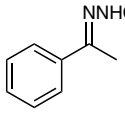
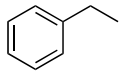
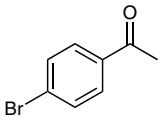
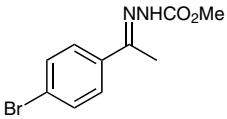
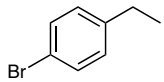
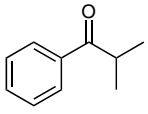
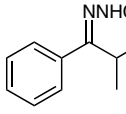
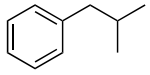
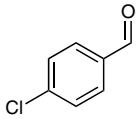
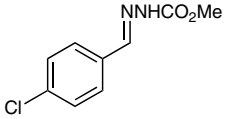
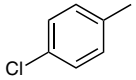
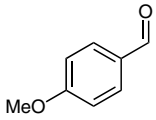
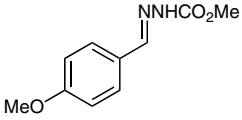
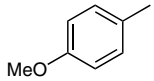
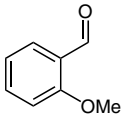
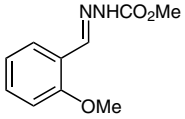
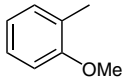
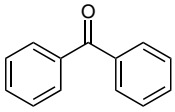
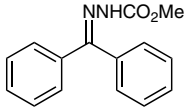
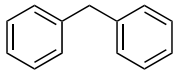
1			96		70[c]
2			80		76
3			96		53
4			79		76
5			77		76
6			65		quant.
7			57		67

Table 1 (continued)

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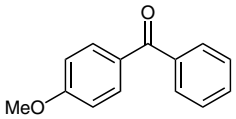
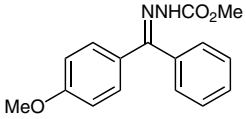
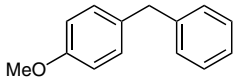
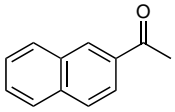
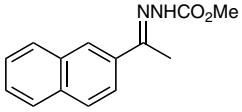
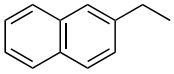
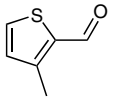
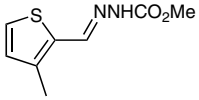
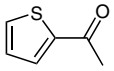
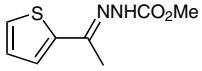
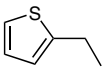
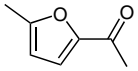
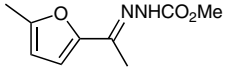
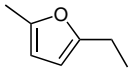
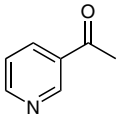
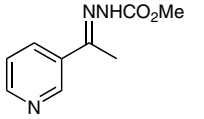
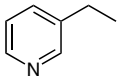
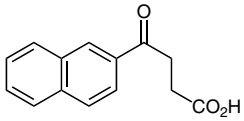
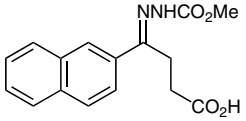
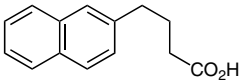
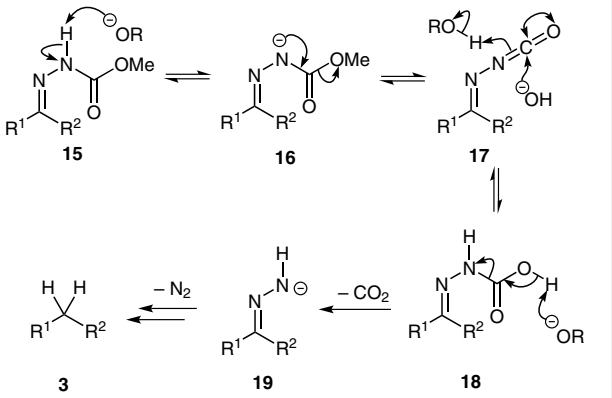
8			55 (87 brsm)		87
9			60		86
10			57		77
11			82		77
12			89		69
13			70		76
14			96		69[d]

[a] Performed using General Procedure 1.
[b] Performed using General Procedure 2.
[c] Reaction was performed on an 8 g scale of the intermediate carbomethoxyhydrazone with 6 equiv of KOH.
[d] Reaction conditions: 5 equiv of KOH were used, and the reaction was heated at 140 °C overnight.

An important class of substrates for the Wolff–Kishner reduction are the 4-oxobutanoic acids, which are derived from the Friedel–Crafts acylation of aromatic systems with succinic anhydride. Once reduced, these systems can be cyclised in order to append a further ring system, and have found use in many fields, for example, catalyst design and helicines.[27] The hydrazone derivative of 4-(naphthalen-2-yl)-4-oxobutanoic acid was formed in excellent yield, with no further purification necessary (Table 1, entry 14). Reduction required an additional equivalent of KOH and heating overnight to form the desired butanoic acid in good yield.

We believe the success of our protocol is due to the ease with which we can form the hydrazine anion **19** (Scheme 3). Under high temperatures, formation of amino isocyanates **17** is well-known.[26] These highly electrophilic species can be expected to undergo addition by hydroxide, followed by irreversible expulsion of carbon dioxide resulting in formation of the requisite amide **19**. This is in agreement with our practical observations where initial effervescence is seen soon after addition of the carbomethoxyhydrazone; however, the reduction and nitrogen-extrusion step is much slower, and therefore rate-determining.



Scheme 3 The proposed mechanistic pathway

In conclusion a simple, safe, and cheap method for the conversion of ketones and aldehydes into their corresponding methylene has been disclosed. Significant safety advances have been made, reducing exposure to the volatile, suspect carcinogenic and teratogenic hydrazine. The interception of the classical Wolff–Kishner intermediate means that this protocol can be easily adapted to previously described examples that have utilised hydrazine.

Acknowledgment

Use of the Chemical Analysis Facility (CAF) at the University of Reading is gratefully acknowledged.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560805.

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(1) All authors contributed an equal amount of work.
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(26) (a) Garland, K.; Gan, W.; Depatie-Sicard, C.; Beauchemin, A. M. *Org. Lett.* **2013**, *15*, 4074. (b) Lavergne, K.; Bongers, A.; Betit, L.; Beauchemin, A. M. *Org. Lett.* **2015**, *17*, 3612.
(27) Wiznycia, A. V.; Desper, J.; Levy, C. J. *Chem. Commun.* **2005**, 4693.
(28) **General Procedure 1**
To the aldehyde or ketone (1.0 g) in EtOH (5–10 mL) was added methyl hydrazinocarboxylate (1.3 equiv) followed by a few drops of AcOH. The reaction was heated at reflux overnight and then cooled to r.t. The product was either purified by recrystallization by dropwise addition of H_2O, cooling upon ice, and collection of the product by Büchner filtration, or the solvent was removed in vacuo and the crude product purified by flash column chromatography to give the carbomethoxyhydrazones.
General Procedure 2
KOH (4 equiv)* was dissolved in triethylene glycol (5 mL) and the solution was heated to 100 °C, forming an orange solution. The carbomethoxyhydrazone (0.5 g) was added in one portion, and the reaction was further heated at 140 °C for 4 h after which time the reaction was cooled, diluted with H_2O, and extracted with Et_2O. The organic phase was dried ($MgSO_4$), filtered, and the solvent removed in vacuo. The crude product was purified by flash column chromatography to provide the desired products as pale yellow oils. *Add one more equivalent KOH per acidic group present.
Representative Data for Methyl (*E*)-2-[1-(4-Bromophenyl)ethylidene]hydrazine-1-carboxylate (Table 1, entry 2)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (1 H, br s, NH), 7.63 (2 H, d, *J* = 8.8 Hz, CH_{Ar}), 7.49 (2 H, d, *J* = 8.8 Hz, CH_{Ar}), 3.88 (3 H, s, OCH_3), 2.19 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.5 (C=N), 136.8 (C_{Ar}Br), 131.6 (C_{Ar}H), 127.9 (C_{Ar}H), 123.6 (C_{Ar}), 53.3 (OCH_3), 12.7 (CH_3). IR (neat): ν_{max} = 3196, 2945, 1730, 1702, 1539, 1484 cm^{-1}. HRMS (ESI$^+$): *m/z* was calcd for $C_{10}H_{12}O_2N_2{}^{79}Br$: 271.0077 [M + H]$^+$; found: 271.0077. Mp 152–155 °C (EtOH).
Representative Data for 1-Bromo-4-ethylbenzene (Table 1, entry 2)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (2 H, d, *J* = 8.4 Hz, CH_{Ar}), 7.06 (2 H, d, *J* = 8.4 Hz, CH_{Ar}), 2.59 (2 H, q, *J* = 7.6 Hz, CH_2CH_3), 1.21 (3 H, t, *J* = 7.6 Hz, CH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.2 (C_{Ar}), 131.3 (C_{Ar}H), 129.6 (C_{Ar}H), 119.3 (C_{Ar}Br), 28.3 (CH_2CH_3), 15.5 (CH_2CH_3). IR (neat): ν_{max} = 3022, 2963, 2928, 2871, 1485 cm^{-1}.