Organic LETTERS

Letter

pubs.acs.org/OrgLett

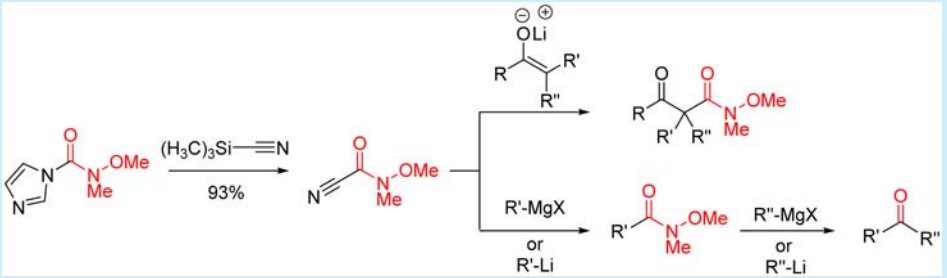
N-Methoxy-*N*-methylcyanoformamide, a Highly Reactive Reagent for the Formation of β-Keto Weinreb Amides and Unsymmetrical Ketones

Jeremy Nugent[†] and Brett D. Schwartz*[,†,‡]

[†]Research School of Chemistry, Institute of Advanced Studies, The Australian National University, Canberra, ACT 2601, Australia

[‡]Eskitis Institute for Drug Discovery, Griffith University, Don Young Road, Nathan, QLD 4111, Australia

Supporting Information



ABSTRACT: A rapid and straightforward synthesis of the new and highly reactive reagent *N*-methoxy-*N*-methylcyanoformamide from trimethylsilyl cyanide and *N*-methoxy-*N*-methylcarbamoylimidazole, is reported. This reagent enables the one-pot preparation of β-carbonyl Weinreb amides from lithium enolates, one-carbon homologated Weinreb amides, and unsymmetrical ketones in one-pot procedures from various organometallic species.

The vast synthetic utility of Weinreb amides[1] has led to a significant amount of research into methods of synthesizing compounds bearing this functionality.[2] Weinreb amides are usually synthesized from the corresponding activated carboxylic acid equivalents[2] or are installed directly from an organometallic species and an *N*-methoxy-*N*-methylcarbamoyl electrophile such as **1**,[3] **2**,[4] or **3**[5] (Figure 1).

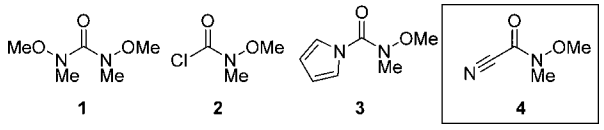
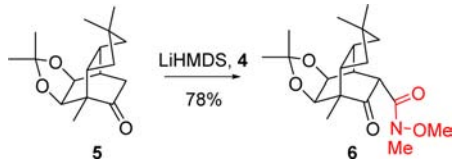


Figure 1. *N*,*O*-dimethylcarbamoylating reagents.

β-Keto Weinreb amides are commonly encountered intermediates in organic synthesis.[6] A recent synthetic study in our laboratory involved the conversion of ketone **5**[7] to the corresponding β-keto Weinreb amide **6** (Scheme 1). During our investigation, we discovered that the reaction of the lithium enolate of **1** with common *N*-methoxy-*N*-methylcarbamoylating reagents such as **1** and **2** either did not proceed or resulted in *O*-carbamoylation. Surprisingly, despite Mander's pioneering work[8] using methyl cyanoformate for the selective *C*-carbomethoxylation of enolates, a direct transformation from ketones to the β-keto Weinreb amides has not been described. Accordingly, we focused on synthesizing and using the previously unreported Mander-type cyanoformamide **4**.

Scheme 1. Direct Transformation of Ketone 5 to β-Keto Weinreb Amide 6

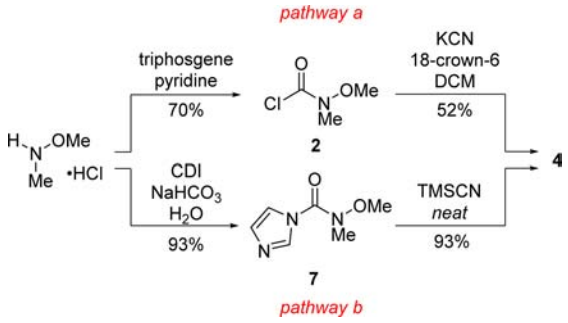


Initially, access to **4** was achieved using conditions reported by Weber[9] for the synthesis of isobutyl cyanoformate. Thus, exposure of *N*-methoxy-*N*-methylcarbamoyl chloride (**2**)[4c] to potassium cyanide in DCM resulted in the formation of **4** (Scheme 2, pathway a). The lithium enolate derived from **5**, formed upon exposure to LiHMDS, reacted rapidly at −78 °C with **4** to provide the desired β-keto Weinreb amide **6** in 78% yield with >99% *dr*. The moderate yields associated with the synthesis of **4** and the use of triphosgene prompted us to explore a more practical and scalable procedure. An assessment of the literature revealed few examples detailing the preparation of cyanoformamides,[10] the majority of which were unsuitable for scale-up. Sarpong's report[11] of the use of imidazole carbamoylating urea reagent **7** encouraged us to use this as a more accessible alternative to *N*-methoxy-*N*-methylcarbamoyl chloride. To access **7**, we opted to use a modification of

Received: June 24, 2016
Published: July 19, 2016

DOI: 10.1021/acs.orglett.6b01844
Org. Lett. 2016, 18, 3834−3837

Scheme 2. Synthesis of *N*-Methoxy-*N*-methylcyanoformamide (4)



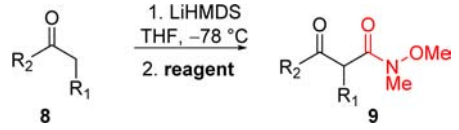
Padiya's "In Water" imidazole carbonylation procedure[12] (Scheme 2, pathway b), thus generating the required urea conveniently, rapidly, and in high yield.

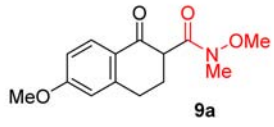
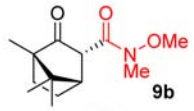
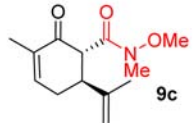
The synthesis of **4** from **7** required a cyanide source, and the restrictions imposed on access to inorganic cyanides encouraged the use of readily available trimethylsilyl cyanide (TMSCN). A number of conditions were screened for the condensation of **7** with TMSCN in various solvents, but excellent yields were only obtained using a "green", anhydrous, solvent-free mixture. This reaction is amenable to scale-up and can be performed with only 1.05 equiv of TMSCN at 18 °C for 18 h or similarly for 10 min at 100 °C in 93% yield. Efforts to isolate **4** directly from the reaction flask by fractional distillation were unfortunately hampered by contamination of 1-trimethylsilylimidazole, which shares a similar boiling point. To avoid this issue, the reaction was quenched with an aqueous workup prior to isolation.[13] *N*-Methoxy-*N*-methylcyanoformamide is a colorless oil after distillation (bp 81−84 °C, 19 mmHg) and should be stored under an inert atmosphere. While we did not notice appreciable degeneration of the reagent after storage in a Schlenk flask under inert, anhydrous conditions for 2 months at room temperature, we recommend storage below 0 °C. Care must be taken to avoid exposure to **4**, especially via inhalation and skin contact, and it should be treated as highly toxic, as the reagent decomposes slowly in water/moist air, presumably to liberate HCN, CO_2, and *N*,*O*-dimethylhydroxylamine, the last of which can react slowly with **4** to form the symmetrical urea **1**.[14]

With an efficient synthesis of **4** in hand, we initiated a comparison study of this reagent with the recently reported *N*-methoxy-*N*-methylcarbamoylpyrrole (**3**)[5] and imidazole reagent **7** in regard to their ability to react with lithium enolates to directly synthesize *β*-keto Weinreb amides (Table 1). All of the carbamoylating reagents were successful in converting 6-methoxy-1-tetralone to **9a** (entry 1), but the reactions involving reagents **3** and **7** both required extended reaction times and warming to room temperature. In contrast, reactions with **4** were complete within 15 min at −78 °C. In the case of hindered ketones (entries 2 and 3) only cyanoformamide **4** efficiently formed the product Weinreb amides (**9b** and **9c**) in high yields.[15]

We next turned to an investigation of the substrate scope of cyanoformamide **4** for the formation of *β*-carbonyl Weinreb amides. We subjected the reagent to a variety of lithium enolates (Scheme 3) and discovered that enones (**8c−f**), aryl ketones and lactones (**8a**, **8g**, **8h**, **8i**, and **8l**), and saturated cyclic and aliphatic ketones (**8j** and **8k**) were all suitable substrates.[16] These compounds all underwent clean and

Table 1. Screening of *N*-Methoxy-*N*-methylcarbamoyl Reagents 3, 4, and 7 with Lithium Enolates



entry	product	reagent 3[a]	reagent 7[a]	4[b]
1	 9a	71%	66%	**86%**
2	 9b	13% *dr* 95:5	20% *dr* 95:5	**87%** *dr* 95:5
3	 9c	24% *dr* > 99:1	23% *dr* > 99:1	**83%** *dr* > 99:1

[a]Reaction conditions: **8** (1.0 mmol), LiHMDS (1.1 mmol), THF, −78 °C, 1 h, then **3** or **7** (1.1 mmol), −78 °C → 18 °C, 20 h. [b]Reaction conditions: **8** (1.0 mmol), LiHMDS (1.1 mmol), THF, −78 °C, 1 h, then **4** (1.1 mmol), −78 °C, 0.25 h.

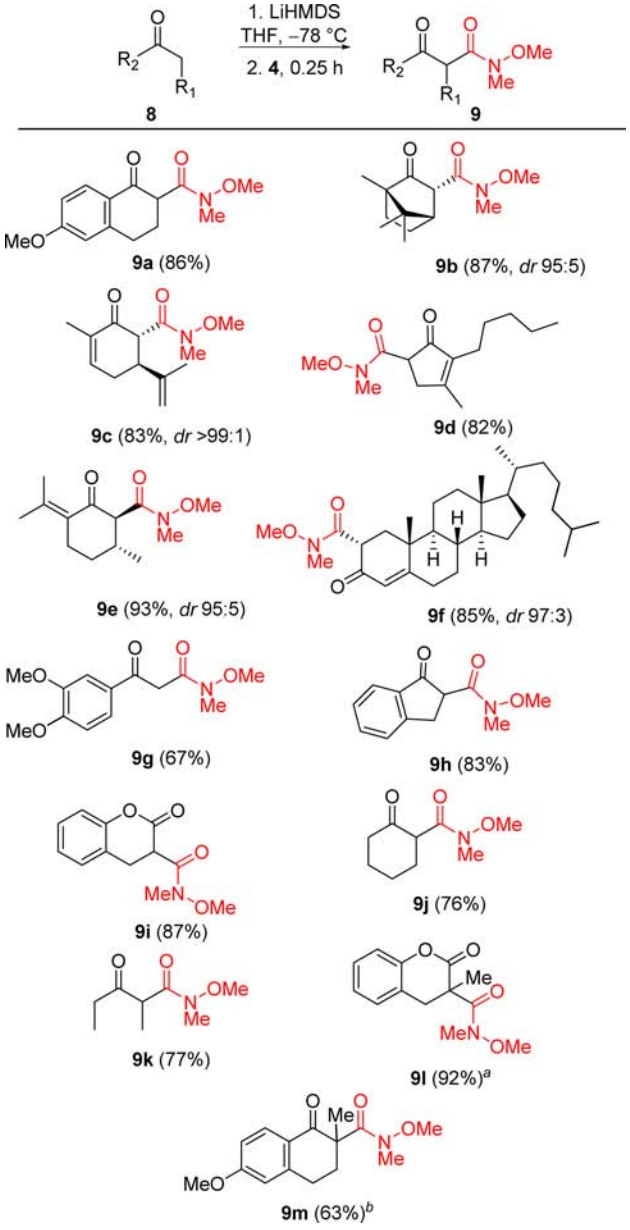
efficient reactions to afford the product *β*-carbonylamides in excellent yields at low temperature. Surprisingly, the major product derived from the reaction of **4** with cyclohexanone, **9j**, was initially found to be the cyanohydrin−product adduct. However, it was discovered that the cyanohydrin could be easily transformed directly into the required *β*-keto Weinreb amide simply by quenching the reaction with aqueous NaOH and stirring at room temperature for 1 h. Unfortunately, under our standard conditions the quaternary products **9l** and **9m** were not observed. In the case of **9l**, deprotonation at 0 °C and addition of **4** at −78 °C allowed efficient product formation. Under our standard conditions, **9m** was not observed, but instead, only the *O*-carbamoylated product was isolated. Extended reaction times at higher temperatures (−40 to 18 °C) resulted in complex reaction mixtures. To alleviate this problem, the reaction was conducted in diethyl ether with the addition of HMPA, which provided good yields of the quaternary product **9m**. The less toxic additive DMPU gave similar results.

We next investigated the ability of **4** to act as a general means to install the Weinreb amide functionality through reaction with various organometallic species. Lithiated species (Table 2, entries 1−3) were highly reactive toward **4** and selective for the single one-carbon-homologated Weinreb amide addition products (**10a−c**). No reaction of **4** with Grignard reagents was observed at −78 °C in THF; however, when the reaction was conducted at 0 °C and with 1 equiv of nucleophile, only the single-addition products (**10a**, **10d**, and **10e**) were observed (entries 4−6). Surprisingly, and in contrast with reagent **3**,[5] the reaction of sp^2-hybridized Grignard reagents with reagent **4** allowed the selective formation of the monoaddition products (**10d** and **10e**).

We predicted that **4** could act as a carbonyl dication synthon[3a,5] in the one-pot formation of unsymmetrical ketones, hence, we subjected **4** to various organometallics in a sequential

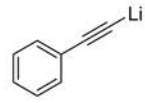
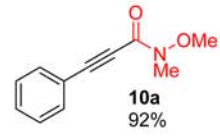
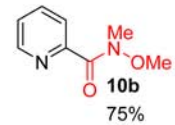
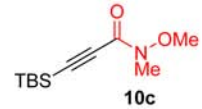
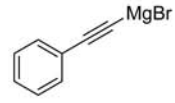
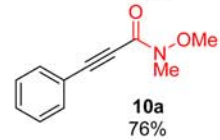
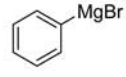
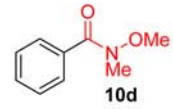
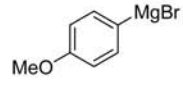
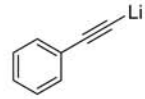
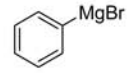
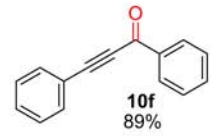
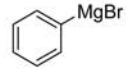
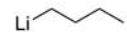
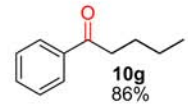
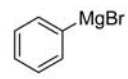
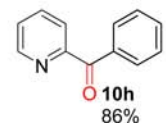
DOI: 10.1021/acs.orglett.6b01844
Org. Lett. 2016, 18, 3834−3837

Scheme 3. Scope of Lithium Enolate Addition to Cyanoformamide 4



[a]Reaction conditions: **8l** (1.0 mmol), LiHMDS (1.1 mmol), THF, 0 °C, 0.5 h, then **4** (1.1 mmol), −78 °C → −40 °C, 0.5 h. [b]Reaction conditions: **8m** (1.0 mmol), LDA (1.1 mmol), Et_2O, −78 °C, 1 h, then 0 °C for 0.25 h, −78 °C, **4** (1.1 mmol), then HMPA (1.0 mmol), −78 °C, 0.5 h.

Table 2. Scope of *N,O*-Dimethylcarbamoylation and Unsymmetrical Ketone Synthesis

entry	first nucleophile	second nucleophile	product[a]
1		-	 **10a** 92%
2		-	 **10b** 75%
3		-	 **10c** 76%
4		-	 **10a** 76%
5		-	 **10d** 92%
6		-	 **10e** 88%
7			 **10f** 89%
8			 **10g** 86%
9			 **10h** 86%

[a]Isolated yields. For reaction conditions, refer to the Supporting Information.

manner (Table 2, entries 7−9). In all three cases we obtained excellent yields of the desired ketones (**10f−h**) regardless of the nature of the first or second nucleophile (i.e., Grignard or organolithium).[5]

In summary, we have reported a very useful reagent for the preparation of *β*-carbonyl Weinreb amides from their respective lithium enolates in excellent yields. *N*-Methoxy-*N*-methylcyanoformamide can also be exposed to reactive organometallic species to afford one-carbon-homologated Weinreb amides or used as a carbonyl dication synthon to prepare unsymmetrical ketones in a highly selective manner. Because of the versatility and reliability of this reagent, it should serve as a useful addition to the synthetic chemist's toolbox.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01844.

Experimental procedures, spectroscopic and analytical data, and NMR spectra of new compounds (PDF)

DOI: 10.1021/acs.orglett.6b01844
Org. Lett. 2016, 18, 3834−3837

AUTHOR INFORMATION

Corresponding Author

*E-mail: brett.schwartz@anu.edu.au. Current address: Research School of Chemistry, Institute of Advanced Studies, The Australian National University, Canberra, ACT 2601, Australia.

Author Contributions

The manuscript was written through contributions of both authors. Both authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors acknowledge Prof. Martin Banwell (The Australian National University), Assoc. Profs. Mark Coster and Rohan Davis (The Eskitis Institute for Drug Discovery, Griffith University), and Dr Andrew Piggott (Macquarie University) for their generosity. B.D.S. is indebted to The National Health and Medical Research Council for financial support (Grant APP1024314), and J.N. is grateful to the Australian Government for an APA Scholarship.

REFERENCES

(1) (a) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815. (b) Pace, V.; Holzer, W.; Olofsson, B. *Adv. Synth. Catal.* **2014**, *356*, 3697. (c) *N*-Acylazetidines have been used in a manner similar to Weinreb amides. See: Liu, C.; Achtenhagen, M.; Szostak, M. *Org. Lett.* **2016**, *18*, 2375.

(2) (a) Nowak, M. *Synlett* **2015**, *26*, 561. (b) Balasubramaniam, S.; Aidhen, I. S. *Synthesis* **2008**, *2008*, 3707. (c) Mentzel, M.; Hoffmann, H. M. R. *J. Prakt. Chem./Chem.-Ztg.* **1997**, *339*, 517.

(3) (a) Whipple, W. L.; Reich, H. J. *J. Org. Chem.* **1991**, *56*, 2911. (b) Hlasta, D. J.; Court, J. J. *Tetrahedron Lett.* **1989**, *30*, 1773.

(4) (a) Murakami, M.; Hoshino, Y.; Ito, H.; Ito, Y. *Chem. Lett.* **1998**, *27*, 163. (b) Krishnamoorthy, R.; Lam, S. Q.; Manley, C. M.; Herr, R. J. *J. Org. Chem.* **2010**, *75*, 1251−1258. (c) Smith, A. B.; Beiger, J. J.; Davulcu, A. H.; Cox, J. M. *Org. Synth.* **2005**, *82*, 147.

(5) Heller, S. T.; Newton, J. N.; Fu, T.; Sarpong, R. *Angew. Chem., Int. Ed.* **2015**, *54*, 9839.

(6) (a) Kumaraswamy, G.; Narayana Murthy, A.; Narayanarao, V.; Vemulapalli, S. P. B.; Bharatam. *Org. Biomol. Chem.* **2013**, *11*, 6751. (b) Calter, M. A.; Liao, W. *J. Am. Chem. Soc.* **2002**, *124*, 13127. (c) Calter, M. A.; Bi, F. C. *Org. Lett.* **2000**, *2*, 1529. (d) Du, H.; Rodriguez, J.; Bugaut, X.; Constantieux, T. *Chem. - Eur. J.* **2014**, *20*, 8458. (e) Inokuchi, T.; Kawafuchi, H. *J. Org. Chem.* **2006**, *71*, 947.

(7) Schwartz, B. D.; Matoušová, E.; White, R.; Banwell, M. G.; Willis, A. C. *Org. Lett.* **2013**, *15*, 1934.

(8) (a) Mander, L.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425. (b) Crabtree, S. R.; Chu, W. L. A.; Mander, L. N. *Synlett* **1990**, *1990*, 169.

(9) Childs, M. E.; Weber, W. P. *J. Org. Chem.* **1976**, *41*, 3486.

(10) (a) Welcher, R. P.; Castellion, M. E.; Wystrach, V. P. *J. Am. Chem. Soc.* **1959**, *81*, 2541. (b) Yang, J. M.; Xiang, D. X.; Zhang, R.; Zhang, N.; Liang, Y. J.; Dong, D. *Org. Lett.* **2015**, *17*, 809. (c) Zhan, Z.; Cheng, X.; Zheng, Y.; Ma, X.; Wang, X.; Hai, L.; Wu, Y. *RSC Adv.* **2015**, *5*, 82800. (d) García-Egido, E.; Paz, J.; Iglesias, B.; Muñoz, L. *Org. Biomol. Chem.* **2009**, *7*, 3991.

(11) Heller, S. T.; Sarpong, R. *Org. Lett.* **2010**, *12*, 4572.

(12) Padiya, K. J.; Gavade, S.; Kardile, B.; Tiwari, M.; Bajare, S.; Mane, M.; Gaware, V.; Varghese, S.; Harel, D.; Kurhade, S. *Org. Lett.* **2012**, *14*, 2814.

(13) ^{1}H and ^{13}C NMR spectral data obtained on the crude reaction mixture confirmed the presence of a 1:1 mixtutre of **4** and 1-trimethylsilylimidazole. See the Supporting Information for details.

(14) The half-life in D_2O at 18 °C is 39 h. If decomposition of **4** is observed, purification by flash chromatography (elution with ether) or distillation can be performed. See the Supporting Information for details.

(15) The stereochemistry was assigned on the basis of a combination of mechanistic expectations and spectral data.

(16) Preliminary results suggest that the lithium enolates derived from simple lactones and lactams react efficiently with reagent **4**.

DOI: 10.1021/acs.orglett.6b01844
Org. Lett. 2016, 18, 3834−3837