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LETTERS

Formylations of anions with a ‘Weinreb’ formamide: *N*-methoxy-*N*-methylformamide

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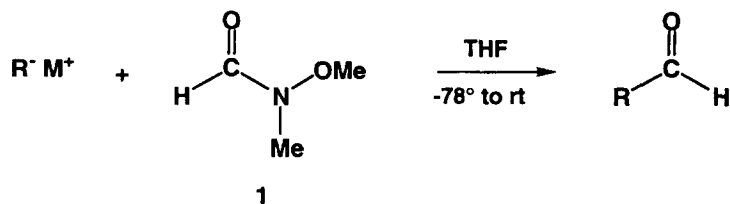
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Abstract

Treatment of organolithiums, Grignard reagents, or enolates with *N*-methoxy-*N*-methylformamide leads to formylated products in good yields without competing secondary processes. © 1999 Elsevier Science Ltd. All rights reserved.

Formylation of a carbanion constitutes a fundamental carbon–carbon bond-forming reaction in organic synthesis, highly valued for the options engendered by the newly introduced acyl moiety.¹ By far the most commonly used reagent for this operation is *N,N*-dimethylformamide (DMF), owing to its ready availability and low cost. Nonetheless, problems with DMF are frequently encountered, in particular due to its tendency to allow for second-stage events resulting from electron transfer, reduction, and/or loss of dimethylamide from a labile tetrahedral intermediate.² Acylations en route to ketones raise identical issues, although such complications have been obviated with the advent of Weinreb amides.^{2c} While numerous modifications at nitrogen in formamide derivatives have been described in the literature over the years,³ curiously, the simple expedient of using *N*-methoxy-*N*-methylformamide (**1**), the formyl analog of Weinreb carboxylic acid amides, has never been examined as a formylating agent. In this Letter, we describe our studies on the use of this readily available amide as an effective means of introducing a formyl group without concern of over-addition to the newly generated aldehyde.

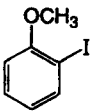
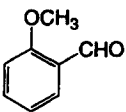
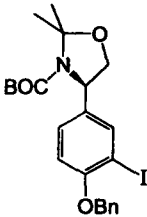
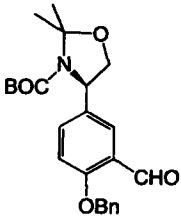
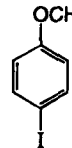
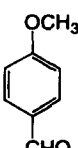
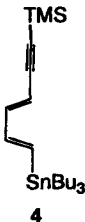

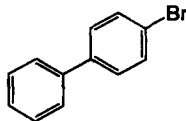
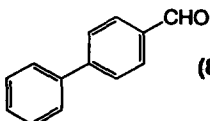
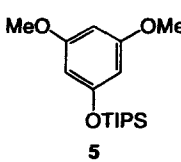
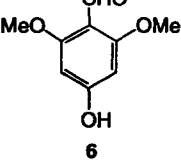
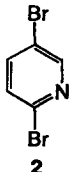
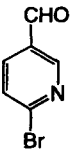
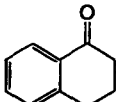
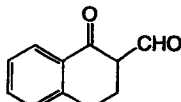
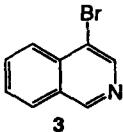
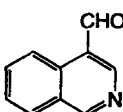
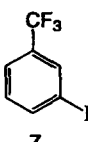
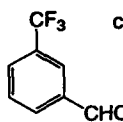
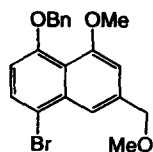
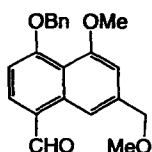


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N-Methoxy-*N*-methylformamide (**1**)⁴ is a clear, colorless liquid (bp 45°C at 9 mmHg) readily prepared from commercially available methyl formate and *O,N*-dimethylhydroxylamine in the presence of NaOMe (vide infra). It is stable at room temperature, and freely soluble in ethereal solvents. Formylations with this material are readily effected by the addition of ca. 1.5 equivalents of **1**, dissolved in THF (ca. 0.2 M), to a -78°C (or colder) solution containing the preformed anion. Warming as necessary followed by quenching and an aqueous acid work-up leads to the aldehydic product.

Several aryllithiums were generated in standard fashion via metal/halogen or Li/Sn exchange on, or direct lithiation of, the substrates illustrated in Table 1. Both *ortho*- and *para*-iodoanisoles (entries

Table 1
Formylations using *N*-methoxy-*N*-methylformamide^{a,b}

substrate	product	yield	substrate	product	yield
(A) 		(91%)	(G) 		(81%)
(B) 		(89%)	(H) 		(89%)
(C) 		(87%)	(I) 		(74%)
(D) 		(60%)	(J) 		(86%)
(E) 		(76%)	(K) 		(86%)
(F) 		(89%)			

^a All new compounds were fully characterized by IR, NMR, MS, and HRMS data.

^b Yields are for isolated, chromatographically purified material. ^c Derived from the corresponding Grignard intermediate.

A, B), as well as more functionalized iodides (entry G), in lithiated form, reacted with essentially equal facility. Aryl bromides, likewise, were converted to their lithio derivatives and formylated in good yields (entries C–F). Representative heteroaromatics (e.g., pyridine **2**⁵ and isoquinoline **3**) do not appear to be problematic. Transmetalation from the unsaturated conjunctive vinyl stannane reagent **4**⁶ to the corresponding organolithium (*n*-BuLi, THF, –90°C, 30 min) followed by formylation afforded the desired dienynal (entry H). Benzaldehyde derivative **6** could be formed via direct, selective *ortho*-lithiation of triether **5**, followed by desilylation (5% aqueous HCl, rt, overnight; entry I). A standard ketone enolate, formed using LDA, was smoothly converted to the 1,3-dicarbonyl derivative (entry J). The representative Grignard reagent derived from aryl iodide **7** (entry K) reacted efficiently as well.⁷ Products resulting from multiple additions to an initially formed (presumed) hemiaminal anion^{2c} were not detected.

Brief comparison formylations of several educts are suggestive of the inherent benefits of employing **1** in place of DMF (Table 2). Thus, lithiation/formylation of each of these substrates (quenching with 2 equivalents or more of DMF), led to noticeably less clean reactions manifested by TLC analyses, as well as lower isolated yields in most cases.⁸ A fifth comparison involving phenyllithium, reported to undergo formylation in 69% yield,³ gave the expected product using **1** to the extent of 81%.

Table 2
Comparison formylation reactions using DMF versus **1**

Entry: (A)	Yield: 81% (vs. 91% with 1)
Entry: (C)	Yield: 88% (vs. 87% with 1)
Entry: (F)	Yield: 68% (vs. 89% with 1)
Entry: (I)	Yield: 71% (vs. 74% with 1)

In summary, use of *N*-methoxy-*N*-methylformamide represents an attractive approach to carbanion formylation.⁹ The reagent offers all of the virtues associated with Weinreb amides, currently favored as acylating agents. Thus, amide **1** is likely to find extensive use in synthesis, in particular where highly reactive organometallics are involved.

Acknowledgements

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8. For Table 2, entry (I), see: Landi, J. J.; Ramig, K. *Synth. Commun.* **1991**, 21, 167.
9. *N*-Methoxy-*N*-methylformamide (**1**): *O,N*-Dimethylhydroxylamine hydrochloride (25.00 g, 0.26 mol) was converted to the free base by adding the hydrochloride to a stirring 1:1 mixture of ethanol:water cooled to 0°C under an atmosphere

of argon. Potassium hydroxide (40.00 g, 0.71 mol) was then added and the solution allowed to stir for 10 min. It was then warmed to 42°C and distilled at atmospheric pressure to give 10.85 g (70%) of colorless liquid. To *N,O*-dimethylhydroxylamine (10.85 g, 0.18 mol) in dry diethyl ether (250 mL) at 0°C under an atmosphere of argon was added methyl formate (16.42 mL, 0.27 mol) followed by sodium methylate (12.21 g, 0.27 mol). The solution was stirred for 2 h at 0°C, then filtered through a thin layer of sand on a fritted funnel to remove salts. The filtrate was fractionally distilled, with *N*-methoxy-*N*-methylformamide being collected at 45°C (9 mmHg); 13.08 g (83%), as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ: 2.96 (s, 3H), 3.69 (s, 3H), 7.80 (s, 1H), 8.20 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ: 30.45, 33.89, 60.98, 63.07, 157.46, 162.41; IR 1680 cm⁻¹; LREIMS *m/z* (rel int): 89 (22), 61 (20), 60 (17), 59 (80), 46 (100) 45 (12); HREIMS calcd for C₃H₇NO₂: 89.0478; found: 89.0477. Representative formylation with **1** (Table 1, entry E): 4-bromoisquinoline (300 mg, 1.44 mmol) was weighed into an oven dried 25 mL round bottomed flask equipped with a stir bar and septa and purged with argon. Diethyl ether (8 mL) was added and the solution was cooled to -78°C and stirred for 5 min. *n*-BuLi in hexanes (0.64 mL, 2.46 M) was added dropwise via syringe to the stirring solution. After 5 min, *N,O*-dimethylhydroxyformamide (192.4 mg, 2.2 mmol) in diethyl ether (1 mL) was added dropwise to the reaction flask via cannula and allowed to stir for another 15 min at -78°C. The reaction mixture was then warmed to 0°C with an ice bath and stirred at this temperature for 1 h. The reaction was then quenched with 5% aqueous HCl until the pH was 2–3. The aqueous layer was extracted with diethyl ether (3×10 mL), the organics were combined and dried over anhydrous Na₂SO₄, and then the organics were removed in vacuo. The product was purified by column chromatography on silica gel (30% EtOAc in hexanes) to give 173 mg (76%) of a white solid; mp 100–102°C, ¹H NMR (400 MHz, CDCl₃) δ: 7.74–7.78 (m, 1H), 7.92–7.96 (m, 1H), 8.09–8.11 (m, 1H), 8.95 (s, 1H), 9.21–9.23 (m, 1H), 9.45 (s, 1H), 10.41 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ: 124.66, 125.05, 128.55, 128.57, 128.64, 132.56, 133.78, 153.17, 158.57, 193.07; IR 1693 cm⁻¹; LREIMS *m/z* (rel int): 158 (15), 157 (100), 156 (48), 129 (43), 128 (84), 102 (30), 101 (22), 77 (15), 76 (11), 75 (28), 74 (19), 51 (30), 50 (23); HREIMS calcd for C₁₀H₆NO: 157.0522; found: 157.0528.