An Unexpected Equilibrium Process Associated with a Standard Approach to Ynone Synthesis

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Abstract: A direct comparison between Weinreb amides and morpholine amides was made with regard to their reactions with alkynyllithium reagents to form ynones. While treatment with stoichiometric alkynyllithium generally effects complete reaction in the case of Weinreb amides, incomplete reactions are obtained from the corresponding morpholine amides. This difference is attributed to an unexpected equilibrium process in the latter case, and it is shown that the use of excess alkynyllithium reagent with morpholine amides provides a synthetically useful synthesis of ynones at 0 °C.

Although somewhat unstable as a general class, ynones are useful intermediates in the synthesis of a variety of heterocycles including isoxazoles and pyrazoles.[1] One commonly used method for ynone preparation is the addition of alkynyllithium reagent, usually in excess, to a Weinreb amide in THF, usually at low temperatures.[2] Our interest in the synthesis of ynones arose from the need to replace a Weinreb amide intermediate with a more stable, easily prepared substitute.[3] A search of the literature indicated that morpholine amides may be used to replace Weinreb amides in ketone synthesis,[4] but in only one reference is this applied to an ynone.[4f] The reported reaction is performed at −78 °C with 3 equiv of an alkynyl borane.[4g] Although not ideal for our purposes, this report encouraged us to pursue the use of morpholine

TABLE 1. Use of Weinreb Amides at 0 °C

		amide		alkyllithium		products[a]	
						% AUC	% AUC
entry	**1**	R	**2**	R′-Li	**3**	ketone	byproduct
1	**1a**	PhCH₂CH₂	**2a**	BuC≡CLi	**3a**	>99	0
2	**1a**	PhCH₂CH₂	**2b**	PhC≡CLi	**3b**	>99	0
3	**1a**	PhCH₂CH₂	**2c**	BuLi	**3c**	77	7[b]
4	**1b**	Ph	**2a**	BuC≡CLi	**3d**	>99	0
5	**1b**	Ph	**2b**	PhC≡CLi	**3e**	>99	0
6	**1b**	Ph	**2c**	BuLi	**3f**	69	17[b]

[a] As analyzed by HPLC; area under the curve (AUC) is measured at 220 nm. Structures confirmed by NMR and LC/MS. *[b]* Consistent with loss of methoxy group by LC/MS.

amides in ynone synthesis. Ultimately, we developed a process that permitted the replacement of our specific Weinreb amide with its morpholine amide counterpart to produce the desired ynone at 0 °C without the use of an alkynyl borane derivative. This success prompted us to develop a general method that might not have scale limitations. During the course of our studies, we uncovered unexpected differences between the behavior of Weinreb amides and morpholine amides.

The addition of alkynyllithium reagents to Weinreb amides at 0 °C was examined. It was determined that approximately 1 equiv of alkynyllithium is sufficient for complete conversion to the ynone. For example, when amide **1a** is added to 1.1 equiv of alkynyllithium **2a** at 0 °C and stirred for 1 h, ynone **3a** is observed after transferring the resulting mixture into AcOH/MeOH/water (Table 1, entry 1). It is important that the reaction mixture is added to an acidic solution (and not vice versa) due to the base lability of the ynone product. These reaction conditions hold true for all pairings of Weinreb amides with alkynyllithium reagents as indicated in entries 1, 2, 4, and 5. While this observation constitutes a significant step forward for practical ynone synthesis, there still remain compelling safety reasons to avoid the use of Weinreb amides, at least as a general class, on scale.[3] Incidentally, 0 °C is not a suitable temperature for the reaction of Weinreb amides with more basic organolithium reagents such as butyllithium (entries 3 and 6).[5]

The performance of morpholine amides at 0 °C was similarly assessed. In this case incomplete reaction was consistently observed (Table 2) when conditions analogous to those used with the Weinreb amides were employed.[6] For example, when amide **4a** is added to 1.1 equiv of alkynyllithium reagent **2a** at 0 °C, and after 1 h the resulting mixture is transferred to the acidic medium

(1) (a) Wang, X.; Tan, J.; Zhang, L. *Org. Lett.* **2000**, *2*, 3107. (b) Utimoto, K.; Miwa, H.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 4277. (c) Arcadi, A.; Marinelli, F.; Rossi, E. *Tetrahedron* **1999**, *55*, 13233. (d) Hojo, M.; Tomita, K.; Hosomi, A. *Tetrahedron Lett.* **1993**, *34*, 485.

(2) (a) Dixon, D. J.; Ley, S. V.; Tate, E. W. *Synlett* **1998**, 1093. (b) Molander, G. A.; McWilliams, J. C.; Noll, B. C. *J. Am. Chem. Soc.* **1997**, *119*, 1265. (c) Trost, B. M.; Schmidt, T. *J. Am. Chem. Soc.* **1988**, *110*, 2301. (d) In the original paper on *N*-methoxy-*N*-methylamides the synthesis of an ynone is reported with 1.1 equiv of alkynyllithium at 65 °C. Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.

(3) *N,O*-Dimethylhydroxylamine hydrochloride decomposes with the liberation of 1.5 kJ/g. The free base begins thermal decomposition at ∼50 °C. For a report of a fatal explosion due to detonation of the related, high-energy compound, hydroxylamine, see *Chem. Eng. News* **1999**, Aug 16, 23.

(4) (a) Sengupta, S.; Mondal, S.; Das, D. *Tetrahedron Lett.* **1999**, *40*, 4107. (b) Brown, J. D. *Tetrahedron: Asymmetry* **1992**, *3*, 1551. (c) Tasaka, A.; Tamura, N.; Matsushita, Y.; Kitazaki, T.; Hayashi, R.; Okonogi, K.; Itoh, K. *Chem. Pharm. Bull.* **1995**, *43*, 432. (d) Monteith, M. J.; Bailey, K. D.; Crosby, J. PCT Int. Appl. WO 9954272, 1999. (e) Gomtsyan, A. *Org. Lett.* **1999**, *2*, 11. (f) Martin, R.; Romea, P.; Tey, C.; Urpí, F.; Vilarrasa, J. *Synlett*, **1997**, 1414 (g) The method was originally reported for *N,N*-dimethylamides and *N*-methyl-*N*-phenylamides. Yamaguchi, M.; Waseda, T.; Hirao, I. *Chem. Lett.* **1983**, 35.

(5) At this temperature, a major byproduct forms as well as multiple lower level impurities. We speculate that this observation is the origin of the excessive care that has historically been taken in the conversion of Weinreb amides to ynones.

TABLE 2. Use of Morpholine Amides at 0 °C

	amide		alkyllithium		products[a]		
						% AUC	% AUC	% AUC
entry	**4**	R	**2**	R′-Li	**3**	ketone	byproduct	**4**
1	**4a**	PhCH$_2$CH$_2$	**2a**	BuC≡CLi	**3a**	75	0	25
2	**4a**	PhCH$_2$CH$_2$	**2b**	PhC≡CLi	**3b**	42	0	58
3	**4a**	PhCH$_2$CH$_2$	**2c**	BuLi	**3c**	34	22	37
4	**4b**	Ph	**2a**	BuC≡CLi	**3d**	94	0	6
5	**4b**	Ph	**2b**	PhC≡CLi	**3e**	70	0	30
6	**4b**	Ph	**2c**	BuLi	**3f**	96	4	0

[a] As analyzed by HPLC, area under the curve (AUC) is measured at 220 nm. Structures confirmed by NMR and LC/MS.

specified, 25% AUC of the starting amide is observed by HPLC (entry 1). Longer reaction times do not increase conversion. Although reactions of morpholine amides with alkynyllithium reagents do not go to completion, the reactions appear to proceed cleanly with no detectable impurities by HPLC. As in the case of Weinreb amides, the reaction with butyllithium produces a major byproduct (entries 3 and 6). It is worth noting that in the case of aryl amides the morpholine amide outperforms the Weinreb amide on treatment with butyllithium at 0 °C (ca. Table 1 entry 6 versus Table 2 entry 6).

Due to the incomplete conversion to product, there arose the possibility that morpholine amides and alkynyllithium reagents are in equilbrium with their corresponding adducts. By measuring the ynone/amide ratios using HPLC with an internal standard, the existence of an equilibrium process was demonstrated. As would be expected for equilibrium, the ynone/amide ratio obtained after quenching proved to be temperature dependent. For example, when a mixture of amide **4a** and alkynyllithium **2a** is brought to a steady state at 0 °C (i.e., the quenched ynone/amide ratio remains constant over time, ~1 h), the ynone/amide ratio is 3:1 (Table 3, entry 1). When the mixture is warmed to 20 °C and stirred for an additional 1 h the ratio decreases to 2:1. Conversely, when the same mixture is cooled to −20 °C and allowed to achieve a steady state (~2 h), this ratio increases to 4:1. This behavior is observed for most pairings of morpholine amides and alkynyllithium reagents (note that in entry 2 the ratio at 0 °C approaches 1:1 and therefore it is unclear what would be expected from warming or cooling).

It was recognized that identification of a competitive reactant that could cleanly consume amide **4** or alkynllithium **2** and thereby drive the reaction back toward starting materials would secure characterization of the proposed equilibrium. Weinreb amides proved to be ideal competitive reactants as previously demonstrated by their complete reactions with alkynyllithium reagents.[7] When a mixture of morpholine amide **4b** and alkynyllithium **2a** is stirred for 1 h at 0 °C, cooled to −20 °C, stirred for an additional 2 h, and then quenched, ynone

3d is observed in an 18:1 ratio versus amide **4b** (Table 3, entry 3). If, however, this −20 °C mixture is treated with Weinreb amide **1a** prior to quenching, warmed to 0 °C, stirred for 1 h, and then quenched, ynone **3a** becomes the only ynone detected, and morpholine amide **4b** is cleanly regenerated (Scheme 1). This experiment was carried out for all four −20 °C entries in Table 3, and the same phenomenon was observed, clearly demonstrating an equilibrium process.[8]

With the equilibrium behavior qualitatively characterized, it follows that a synthetically viable process could be developed at 0 °C through the use of excess alkynyllithium and, indeed, this is the case (Table 4). For example, in entry 1 the ynone/amide ratio increased from 3:1 (1 equiv of **2a**) to 61:1 (3 equiv) to 135:1 (5 equiv). Even the ~1:1 mixture exhibited when amide **4a** and alkynyllithium **2b** are stoichiometrically combined is boosted to a synthetically useful ratio of 23:1 by use of 5 equiv of alkynyllithium (entry 2). Due to the known instability of ynones, the generated product would ideally be used in a subsequent step without isolation, but it is possible to obtain good isolated yields, when necessary, through the use of chromatography on alumina.

There is an important limitation to the preparative use of morpholine amides in ynone synthesis. Specifically, α-alkyl-substituted morpholine amides may not be used in practical ynone synthesis since the equilibrium lies too far to the side of the amide. For example, when 4-(2-ethylbutanoyl)morpholine was subjected to **2a** (3 or 5 equiv), ynone/amide ratios of <0.2:1 were obtained. Presumably this is a simple steric effect in which the electronically stabilized adduct becomes too crowded (i.e., destabilized) for it to compete energetically with the amide and alkynyllithium mixture. This sensitivity to α-alkyl substitution appears to be unique to the morpholine amides as Weinreb amides of this type do convert to ynones when treated with alkynyllithium reagents.[9]

We conclude that alkynyllithium reagents and morpholine amides, when stirred together, are in equilibrium with their corresponding adduct[10] and that appropriate choice of stoichiometry and temperature allows for preparative use of morpholine amides in ynone synthesis. Furthermore, we suggest that comparative ease of synthesis and the relative thermal stability might be advantages of morpholine amides over Weinreb amides when large-scale preparation is necessary. In contrast, the principle advantage of Weinreb amides is that they may be used in ynone synthesis with a single equivalent of alkynyllithium reagent.

(6) This behavior has been noted for *N,N*-dimethylamides. Verkruijsse, H. D.; Heus-Kloos, Y. A.; Brandsma, L. *J. Organomet. Chem.* **1988**, *338*, 289–294.

(7) When the equilibrium mixtures were treated with butyllithium (to consume the amide), the results were consistent with equilibrium, but multiple impurities complicated analysis and rendered the data less conclusive than desired. Use of pivalaldehyde (to consume the alkynyllithium) was also consistent, but with similar problems.

(8) Under forcing conditions, Weinreb amides also show evidence of reversibility, but the equilibrium constant is presumably so large that reaction reversal becomes synthetically irrelevant.

(9) For examples of alkynyllithium additions to α-alkyl substituted Weinreb amides, see Masquelin, T.; Obrecht, D. *Tetrahedron Lett.* **1994**, *35*, 9387. Trost, B. M.; Schmidt, T. *J. Am. Chem. Soc.* **1988**, *110*, 2301.

(10) For a related phenomenon in which 2,2-dimethylpropargyl alcohols are thermally deprotected to produce acetone and a terminal alkyne, see Boyall, D.; Lopez, F.; Sasaki, H.; Frantz, D.; Carreira, E. M. *Org. Lett.* **2000**, *2* (26), 4233–4236.

TABLE 3. Temperature Dependence of Ynone/Amide Ratio

		amide	alkynyllithium			steady-state yone/amide ratio[a]			
entry	4	R	2	R′C≡CLi	3	−20 °C		0 °C[b] →	20 °C
1	4a	PhCH₂CH₂	2a	BuC≡CLi	3a	4:1	←	3:1 →	2:1
2	4a	PhCH₂CH₂	2b	PhC≡CLi	3b	0.8:1	←	0.9:1 →	0.5:1
3	4b	Ph	2a	BuC≡CLi	3d	18:1	←	12:1 →	5:1
4	4b	Ph	2b	PhC≡CLi	3e	2.2:1	←	1.5:1 →	0.04:1

[a] Product ratios were obtained by HPLC and calculated versus an internal standard. *[b]* Arrows indicate that the ratios reported in the adjacent column were first brought to steady state at 0 °C.
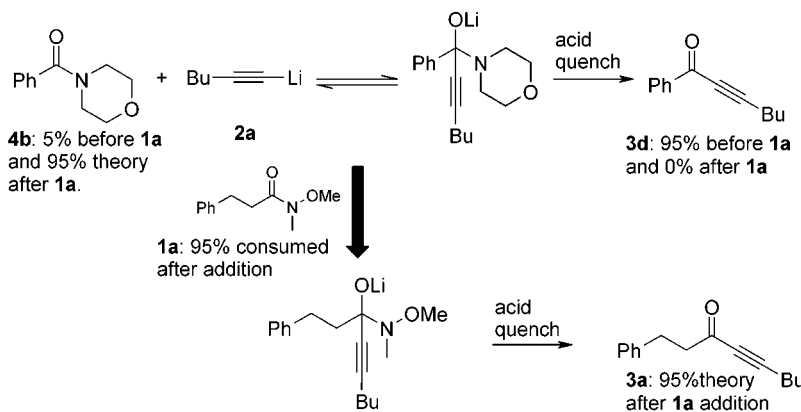
SCHEME 1

TABLE 4. Increase in Ynone/Amide Ratio with Excess Alkynyllithium

		amide	alkynyllithium			ynone/amide ratio vs equiv alkynyl-Li		
entry	4	R	2	R′C≡CLi	3	1 equiv 2	3 equiv 2	5 equiv 2
1	4a	PhCH₂CH₂	2a	BuC≡CLi	3a	3:1	61:1 (80%)[a]	135:1
2	4a	PhCH₂CH₂	2b	PhC≡CLi	3b	1:1	8:1	23:1
3	4a	PhCH₂CH₂	2d	TMSC≡CLi	3g	−	6:1	17:1
4	4b	Ph	2a	BuC≡CLi	3d	12:1	>200:1 (86%)[a]	>200:1
5	4b	Ph	2b	PhC≡CLi	3e	1.5:1	110:1	>200:1
6	4b	Ph	2d	TMSC≡CLi	3h	−	76:1 (71%)[a]	−

[a] Isolated yield after chromatography on neutral alumina.

Experimental Section

General. Unless otherwise noted, starting materials were obtained from commercial suppliers and used without further purification. HPLC analyses were carried out using a Phenomenex Luna 3 μm C18(2) column (50 × 2.0 mm).

General Procedure for Calculation of [Ynone]/[Amide] ratios. The ratio for the **4a** + **2a** equilibrium is described. Amide **4a** (0.52 g, 2.4 mmol) and biphenyl (0.17 g, 1.1 mmol as an internal standard) were dissolved in THF (1.0 mL), and HPLC analysis was used to calculate the initial AUC ratio of **4a** and internal standard. In a separate reaction vessel, 1-hexyne (0.79 mL, 6.8 mmol) and THF (3.0 mL) were introduced into a flask under N₂. After the mixture was cooled to 0 °C, n-BuLi (2.8 mL, 6.9 mmol) was added dropwise over 17 min, thereby generating alkynyllithium **2a**, while maintaining an internal temperature <10 °C. The reaction mixture was stirred at 0 °C for 15 min, and the **4a**/internal standard solution was added. HPLC analysis was performed at 30, 60, and 90 min after addition of the amide solution. HPLC samples were prepared by placing the reaction mixture (0.10 mL) into a solution of 1:1:10 AcOH:H₂O:MeOH (1.0 mL). The resulting quenched solution was diluted further

with methanol prior to injection. The AUC ratio of **4a** to internal standard was measured for each sample by HPLC, and thus the consumption of **4a** could be calculated. This consumption of **4a** was directly attributed to the production of ynone (byproducts were ≪1% for all cases).

1-Phenyl-4-nonyn-3-one (3a). A flask containing 1-hexyne (0.79 mL, 6.8 mmol) was charged with THF (3.0 mL) under N₂. After cooling to 0 °C, n-BuLi (2.8 mL, 6.9 mmol) was added dropwise over 19 min, maintaining an internal temperature <11 °C. The reaction mixture was stirred at 0 °C for 15 min, and then amide **4a** (0.51 g, 2.3 mmol) in THF (1.0 mL) was added. After 60 min at 0 °C, the reaction mixture was transferred via cannula into a solution of AcOH (4.8 mL) and water (2.4 mL) at 0 °C. After 10 min, the organic layer was washed with H₂O, dried over Na₂SO₄, filtered, and concentrated to an oil (0.61 g). Chromatography on neutral alumina (10% EtOAc/hexanes) produced 0.40 g (80%) of **3a**, 99% pure by HPLC analysis. ¹H NMR (300 MHz): δ 0.95 (t, *J* = 7.3, 3H), 1.20−1.64 (m, 4H), 2.39 (t, *J* = 7.0, 2H), 2.86−2.91 (m, 2H), 2.98−3.03 (m, 2H), 7.18−7.37 (m, 5H). ¹³C NMR (75 MHz): δ 13.40, 18.56, 21.87, 29.63, 46.90, 80.77, 94.80, 126.14, 128.14, 128.41, 140.30, 186.98. The NMR spectra are in good agreement with the literature.[11]

1-Phenyl-2-heptyn-1-one (3d). In a procedure analogous to that above, amide **4b** and 3 equiv of alkynyllithium reagent **2a** were combined to prepare ynone **3d** (85% yield, 99% purity by HPLC). ^{1}H NMR (400 MHz): δ 0.97 (t, J = 7.3, 3H), 1.48−1.54 (m, 2H), 1.63−1.70 (m, 2H), 2.51 (t, J = 7.2, 2H), 7.46−7.50 (m, 2H), 7.57−7.61 (m, 1H), 8.13−8.15 (m, 2H). ^{13}C NMR (100 MHz): δ 13.46, 18.86, 22.02, 29.79, 79.63, 96.79, 128.43, 129.49, 133.80, 136.90, 178.20. The NMR spectra are in good agreement with the literature.[12]

1-Phenyl-3-(trimethylsilyl)-2-propyn-1-one (3h). In a procedure analogous to that above, amide **4b** and 3 equiv of alkynyllithium reagent **2d** were combined to prepare ynone **3h** (85% yield, 99% purity by HPLC). ^{1}H NMR (300 MHz): δ 0.33 (s, 9H), 7.47−7.52 (m, 2H), 7.60−7.65 (m, 1H), 8.14−8.17 (m, 2H). ^{13}C NMR (75 MHz): δ 0.00, 101.27, 101.50, 129.26, 130.33, 134.87, 137.14, 178.39. The NMR spectra are in good agreement with the literature.[13]

(11) Mattson, M. N.; Rapoport, H. *J. Org. Chem.* **1996**, *61*, 6071. Note: In the citation the referenced compound (**9g**) is named incorrectly; 1-phenyl-4-heptyn-3-one rather then 1-phenyl-4-nonyn-3-one.

(12) Van den Hoven, B. G.; Bassam, E. A.; Alper, H. *J. Org. Chem.* **2000**, *65*, 4131.

(13) Logue, M. W.; Moore, G. L. *J. Org. Chem.* **1975**, *40*, 131.