Facile KF/Alumina Mediated Synthesis of α-Heterosubstituted Weinreb Amides

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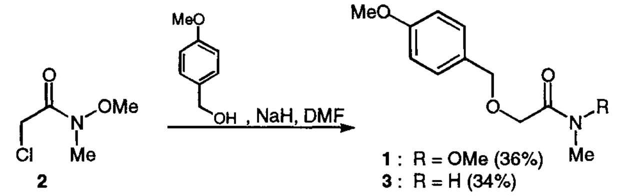
Dedicated to Professor E. J. Corey

Abstract: Anhydrous KF/alumina in dipolar aprotic solvents was found to be an effective promoter in the synthesis of α-heterosubstituted Weinreb amides prepared from 2-chloro-*N*-methoxy-*N*-methylacetamide. This method is high yielding, even for weak nucleophiles, and requires no aqueous workup.

Weinreb amide[1] **1** was required in connection with the synthesis of a series of classical/nonclassical cannabinoid hybrid analogs incorporating a hydroxyl group at C11.[2] Amide **1** was to supply carbon atoms 9 and 11 of the final products. The direct coupling of *p*-methoxybenzyl alcohol and readily available 2-chloro-*N*-methoxy-*N*-methylacetamide **2**[3] was attempted. However, traditional Williamson conditions (Scheme 1) led to the formation of **1** in only 36% isolated yield, accompanied by 34% of methyl amide **3**.[4] Our need for an effective synthesis of **1** promted the present study.



Scheme 1

Loss of the methoxy group from Weinreb amides under basic conditions has been described previously[5] and has proven to be a recurring problem associated with their use.[6] After several silver oxide mediated reactions of *p*-methoxybenzyl alcohol with **2** also failed to produce any of the desired amide, potassium fluoride on alumina (KF/alumina) was tried. The reagent was prepared according to Ando[7a] and the reaction was conducted at 0 °C in acetonitrile. These conditions afforded a clean reaction resulting in a 51% isolated yield of **1** with no unreacted starting material remaining. The reason for the apparent discrepancy in mass balance was determined when the reaction was monitored by ^{1}H-NMR. In addition to participating in the desired reaction, the starting material **2** was apparently undergoing hydrolysis to give volatile *N,O*-dimethylhydroxylamine and chloroacetic acid. Thorough drying of the reagent[8] led to a marked reduction in reactivity, as previously observed by Ando and coworkers.[7b] However, the reaction did proceed to approx. 60% conversion after several days at 50 °C without observable hydrolysis of either starting material or product. Continuous sonication of the reaction mixture resulted in a dramatic increase in the rate.[9] The starting material was consumed after 10 h and **1** was isolated in 73% yield along with 13% of **3**.

Weinreb amides with N,[10a] O,[10b] P,[10c] and S[10d] substituents on the α-carbon have been used in synthesis quite frequently. It was therefore of interest to determine whether the KF/alumina promoted reaction would be generally successful for the preparation of α-heterosubstituted Weinreb amides. The results are summarized in Table I.

Of the oxygen nucleophiles which were examined, only *p*-bromophenol (entry 2) reacted quickly without the aid of sonication. Weak nucleophiles such as benzoic acid (entry 3) required the presence of DMSO and sonication in order for the reaction to proceed at a reasonable rate. The method appears to be unsuitable for chloride displacement from **2** by aliphatic alcohols, since 2-octanol and isobutanol both failed to produce preparatively useful amounts of the desired amides.

Reaction of **2** with diethylphosphite (entry 4) yielded phosphonate **6**, which has been reported by Seidel.[10c] Synthesis of the glycine derivative **7** (entry 5) illustrates another attractive feature of this method. In the past, most α-heterosubstituted Weinreb amides have been prepared from the corresponding acids or esters following protection of the α-functionality. In contrast, this approach allows the α-substituent to be introduced with the amide portion already in place. Reactions with imidazole and indole (entries 6 & 7) gave clean *N*-alkylation. This was not unexpected[12] although low water content in alumina based reagents has been linked to high C-selectivity in alkylation reactions involving other ambident nucleophiles.[13]

Thiophenol and benzyl mercaptan (entries 8 & 9) both reacted rapidly to produce their respective amides **10** and **11** in very high yield. Finally, the reaction of diethyl malonate (entry 10) demonstrated that C-nucleophiles also react with **2** in high yield under these conditions.

Isolation and purification of the products was very easy in all cases: gravity filtration of the reaction mixture through a paper filter, solvent evaporation and either recrystallization or bulb-to-bulb distillation produced the products in high yield. This simple procedure proved to be applicable to all of the listed examples except for **1**, which had to be isolated by column chromatography due to the presence of **3**.

This convenient and high-yielding method for the preparation of α-heterosubstituted Weinreb amides should prove to be of broad synthetic utility.

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References and Notes

(1) Nahm, S.; Weinreb, S, M. *Tetrahedron Lett.* **1981**, *22*, 3815. For a review, see: Sibi, M. P. *Org. Prep. Proc. Intern.* **1993**, *25*, 15.

(2) For recent publications concerning classical/nonclassical cannabinoid hybrid analogs see: Tius, M. A.; Hill, W. A. G.; Zou, X.-L.; Busch-Petersen, J.; Kawakami, J. K.; Fernandez-Garcia, M. C.; Drake, D. J.; Abadji, V.; Makriyannis, A. *Life Sci.* **1995**, *56*, 2007 and references cited therein.

(3) Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001.

(4) Data for methyl amide **3**: mp: 59-61°C ; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.25 (d, J= 8.1 Hz, 2H), 6.89 (d, J= 8.1 Hz, 2H), 6.59 (br s, 1H), 4.48 (s, 2H), 3.95 (s, 2H), 3.80 (s, 3H), 2.82 (d, J= 4.2 Hz, 3H). In addition, ^{13}C, IR, MS and HRMS data was obtained for this compound.

(5) Graham, S. L.; Scholtz, T. H. *Tetrahedron Lett.* **1990**, *31*, 6268. See also: Romo, D.; Johnson, D. D.; Plamondon, L.; Miwa, T.; Schreiber, S. L. *J. Org. Chem.* **1992**, *57*, 5060.

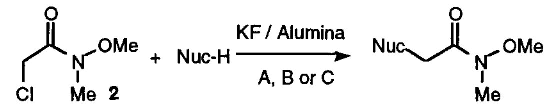
(6) Tius, M. A.; Busch-Petersen, J. Unpublished results.

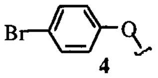
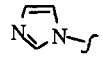
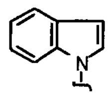
(7) (a) Ando, T.; Yamawaki, J.; Kawate, T.; Sumi, S.; Hanafusa, T. *Bull. Soc. Chem. Jpn.* **1982**, *55*, 2504.
(b) Ando, T.; Kawate, T.; Yamawaki, J.; Hanafusa, T. *Chem. Lett.* **1982**, 935.

(8) The KF/alumina reagent was prepared according to Ando,[7a] however, it was dried overnight at 250 °C (0.2 mmHg).

(9) Ultrasound has previously been reported to enhance the reactivity of KCN/alumina: Ando, T.; Kawate, T.; Yamawaki, J.; Hanafusa, T. *Chem. Lett.* **1984**, 725.

Table I. Weinreb Amides Prepared According to:



Entry	Nuc-H	Nuc	Conditions[a]	Yield	m.p.[b]	^{1}H-NMR (300 MHz, $CDCl_3$) δ[c]
1)	*p*-Methoxybenzyl alcohol	PMBO- **1**	B, 10 h	73%	-	7.32 (d, J= 8.8 Hz, 2H), 6.88 (d, J= 8.8 Hz, 2H), 4.60 (s, 2H), 4,25 (s, 2H), 3.80 (s, 3H), 3.63 (s, 3H), 3.19 (s, 3H).
2)	*p*-Bromophenol	 **4**	A, 14 h	92%	64-65°C	7.34 (d, J= 8.8 Hz, 2H), 6.80 (d, J= 8.8 Hz, 2H), 4.76 (s, 2H), 3.72 (s, 3H), 3.19 (s, 3H).
3)	Benzoic Acid	BzO- **5**	C, 14 h	75%	70-71°C	8.11 (d, J= 8.0 Hz, 2H), 7.56 (t, J= 7.9 Hz, 2H), 7.44 (t, J= 7.9 Hz, 1H), 5.06 (s, 2H), 3.73 (s, 3H), 3.22 (s, 3H).
4)	Diethylphosphite	$(EtO)_2P(O)$- **6**	B, 18 h	80%[10c]	-	4.18 (dq, J= 8.0, 7.1 Hz, 4H), 3.77 (s, 3H), 3.21 (s, 3H), 3.18 (d, J= 24.7 Hz, 2H), 1.34 (t, J= 7.1 Hz, 6H).
5)	Dibenzylamine	Bn_2N- **7**	C, 24 h	83%	-	7.40 (d, J= 7.3 Hz, 4H), 7.33-7.23 (m, 6H), 3.88 (s, 4H), 3.41 (br s, 5H), 3.20 (s, 3H).
6)	Imidazole	 **8**	A, 5 h	91%	77-78°C	7.46 (br s, 1H), 7.02 (br s, 1H), 6.91 (br s, 1H), 4.82 (s, 2H), 3.67 (s, 3H), 3.13 (s, 3H).
7)	Indole	 **9**	B, 13 h	74%	102-103°C	7.67 (d, J= 7.5 Hz, 1H), 7.33-7.14 (m, 4H), 6.60 (d, J= 2.9 Hz, 1H), 5.00 (s, 2H), 3.67 (s, 3H), 3.21 (s, 3H).
8)	Thiophenol	PhS- **10**	A, 3 h	97%	-	7.45 (d, J= 7.3 Hz, 2H), 7.29-7.20 (m, 3H), 3.82 (s, 2H), 3.70 (s, 3H), 3.20 (s, 3H).
9)	Benzyl mercaptan	BnS- **11**	A, 4 h	96%	-	7.39-7.24 (m, 5H), 3.87 (s, 2H), 3.67 (s, 3H), 3.25 (s, 2H), 3.21 (s, 3H).
10)	Diethyl malonate	$(EtO_2C)_2CH$- **12**	A, 36 h	85%	-	4.25-4.16 (m, 4H), 3.91 (t, J= 7.5 Hz, 1H), 3.73 (s, 3H), 3.17 (s, 3H), 3.05 (d, J= 7.5 Hz, 2H), 1.27 (t, J= 7.1 Hz, 6H).

[a] A: CH_3CN, RT ; B: CH_3CN, sonication ; C: CH_3CN / DMSO (2 / 1), sonication.[11]

[b] Products **1**, **6**, **7**, **10**, **11** and **12** were liquids and were purified by bulb-to-bulb distillation.

[c] In addition, ^{13}C, IR, MS and HRMS data was obtained for all products except **6** for which full data has previously been reported.[10c]

(10) (a) Weinreb amides substituted at the α carbon by nitrogen:
Hagihara, M.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 6570.
Edwards, P. D.; Wolanin, D. J.; Andisik, D. W.; Davis, M. W. *J. Med. Chem.* **1995**, *38*, 76.
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(c) Weinreb amides substituted at the α carbon by phosphorus:
Netz, D. F.; Seidel, J. L. *Tetrahedron Lett.* **1992**, *33*, 1957.
See also ref. 3.
(d) Weinreb amides substituted at the α carbon by sulfur:
Selnick, H. G.; Radzilowski, E. M.; Ponticello, G. S. *Tetrahedron Lett.* **1991**, *32*, 721.
Selnick, H. G. Brooks, L. M. *Tetrahedron Lett.* **1989**, *30*, 6607.

(11) **Typical Experimental Procedure C**: KF/alumina reagent (1.7 g, 11.0 mmol) was placed in a three neck round bottomed flask equipped with a mechanical stirrer. The reagent was lightly flame dried at high vacuum (0.2 mmHg) and suspended in 1.4 mL of anhydrous CH_3CN after cooling to RT under argon. Benzoic acid (339 mg, 2.77 mmol) was dissolved in 1.4 mL of anhydrous DMSO. The solution was dried over freshly activated 4Å molecular sieves and transferred by cannula to the KF/alumina reagent. The suspension was stirred mechanically for 5 min at RT. α-Chloroamide **2** (318 mg, 2.31 mmol) was dissolved in 1.4 mL of anhydrous CH_3CN, dried over freshly activated molecular sieves and added to the reaction mixture by cannula. The reaction flask was placed in an ultrasonic cleaning bath and sonicated for 14 h while being stirred mechanically. The KF/alumina reagent was removed by gravity filtration through a paper filter and washed with 4x10 mL of ether. After solvent evaporation (DMSO was removed at 50 °C, 0.2 mmHg) the crystalline crude product was recrystallized from CH_2Cl_2 / ether / hexane to give 385 mg (75% yield) of the Weinreb amide **5**.
(Procedure B: same as procedure C, using CH_3CN in place of