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# Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:

http://www.tandfonline.com/loi/lsyc20

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To cite this article: T. Raghuram , S. Vijaysaradhi , Indrapal Singh & Jaimala Singh (1999) Convenient Conversion of Acid to Weinreb's Amide, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 29:18, 3215-3219, DOI: <u>10.1080/00397919908085946</u>

To link to this article: http://dx.doi.org/10.1080/00397919908085946

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## CONVENIENT CONVERSION OF ACID TO WEINREB'S AMIDE

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Abstract: Various carboxylic acids are converted to their corresponding N-methoxy- N-methyl amides through the mixed anhydride formed by their reaction with pivaloyl chloride.

Since the original discovery of Weinreb<sup>1</sup>, that N-Methoxy-N-methyl amides 1 (now popularly called Weinreb amides) cleanly reacted with Grignard reagents and organolithium to produce ketones, these amides have gained wide importance as very effective acylating agents for various organometallic reagents<sup>2</sup>.

Acid derivatives such as acid halides<sup>3</sup> and esters<sup>4</sup> have been conveniently converted to 1 with ease, but direct conversion of an acid to amide becomes very attractive and important in molecules containing sensitive functionalities.

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Towards this end several acid activating agents have been successful, these include DCC<sup>5</sup>, DEPC<sup>6</sup>, HOBT/DCC<sup>7</sup>, BOP.PF<sub>6</sub><sup>8</sup>, CDI<sup>9</sup>, alkyl chloroformates<sup>10</sup>, CBr<sub>4</sub>/TPP<sup>11</sup>, 2-halo-1-alkylpyridinium salts<sup>12</sup> and py.BOP<sup>13</sup>.

The advantage of the mixed anhydride method wherein the carbonyl groups *differ substantially due to steric factor* has not been put to use for the formation of 1. In this letter , we report a convenient and good yielding procedure for the synthesis of 1 from both chiral and achiral carboxylic acids using extremely cheap and readily available pivaloyl chloride as activating agent (scheme 1). It is clear that at -5°C to O°C, the attack of amine on the pivaloyl carbonyl carbon in the mixed anhydride 2 is precluded due to steric factors and hence good yields of the desired Weinreb amide are obtained. The results are shown in table 1.

**EXPERIMENTAL:** To a stirred solution of the acid (2 mmol) in dry  $CH_2Cl_2$  (5 ml) at -5to 0°C was added  $Et_3N(2.2 \text{ mmol})$  and stirred for 15 min. before pivaloyl chloride(2 mmol) was added. After 1 hr MeO(CH<sub>3</sub>)NH<sub>2</sub>Cl (2 mmol) was added in one lot, followed by dropwise addition of  $Et_3N(4 \text{ mmol})$ . Continued stirring for 1.5 hr (or until disapearance of anhydride, on TLC) at 0 to 5°C and subjected to dilute aq. HCl work up.

Entry	Acid	Product (Weinreb amide)	Yield(%)#
1	ОН	la	73
2	ОН	16	72
3	Слон	lc	79
4	H <sub>3</sub> C SO <sub>2</sub> NHCH <sub>2</sub> COOH	1d	76
5	ОН	1e	82
6	H3CO CH3	lf	72
7		1g	74

Table 1

<sup>#</sup> Isolated yield after chromatography.

For the acid in the entry 7, the optical rotation of the corresponding amide was in agreement with that reported in the literature<sup>14</sup>. The optical purity of the amide corresponding to the acid under entry 6, was determined by the pmr data using chiral shift reagent,  $Eu(hfc)_3$ . The spectral data for the compounds  $1a^{15}$ ,  $1b^1$ ,  $1h^{14}$ , are in agreement with the literature reports.

N-methoxy-N-methyl-pyridine-3-carboxamide (1c). oil, <sup>1</sup>H NMR(60MHz):

 $\delta$ = 3.37(s, 3H); 3.56(s, 3H); 7.31-8.90(m, 4H). IR(CCl<sub>4</sub>): 1657 cm<sup>-1</sup>. Elemental analysis for C<sub>8</sub>H<sub>10</sub>N<sub>2</sub>O<sub>2</sub> calcd C 57.82%, H 6.06%, N 16.86% found C 57.79%, H 6.04%, N 16.80%.

### N-methoxy-N-methyl-N'-p-toluenesulphonylglycinamide (1d).

Oil, <sup>1</sup>H NMR(60MHz):  $\delta = 2.47(s, 3H)$ ; 3.18(s, 3H); 3.73(s, 3H); 5.81(s, 2H), 7.83-

8.2(m,4H).  $IR(CCl_4)$ : 1676 cm<sup>-1</sup>. Elemental analysis for  $C_{11}H_{16}N_2O_4S$ 

calcd C 48.52%, H 5.92%, N 10.29%, S 11.78% found C 48.49%, H 5.89%, N 10.20%, S 11.70%

N-methoxy-N-methyl-3-benzoylpropanamide (1e). oil, <sup>1</sup>H NMR(400MHz):

 $\delta$ = 2.85(t,J=8Hz, 2H); 3.18(s, 3H); 3.3(t, J=8Hz, 2H); 3.78(s, 3H); 7.4-8.0(m, 5H) IR(CCl<sub>4</sub>): 1676 cm<sup>-1</sup>. Elemental analysis for C<sub>12</sub>H<sub>15</sub>NO<sub>3</sub> calcd C 65.14%, H 6.83%, N 6.33%, found C 65.10%, H 6.80%, N 6.32%,

(S)-N-methoxy-N-methyl- $\alpha$ -(6-methoxy-2-naphthyl) propanamide (1f). oil, <sup>1</sup>H NMR(400MHz):  $\delta$ = 1.50(d, J-7.3Hz, 3H); 3.17(s, 3H); 3.39(s, 3H); 3.90(s, 3H); 4.28(bs,1H); 7.10-7.70(m, 6H) IR(CCl<sub>4</sub>) 1667cm<sup>-1</sup>.

Elemental analysis for C<sub>16</sub>H<sub>19</sub>NO<sub>3</sub> calcd C 70.31%, H 7.01%, N 5.12%, found C 70.26%, H 7.00%, N 5.08%.

#### ACKNOWLEDGMENT

SV and I.Singh thank CSIR, (New Delhi) for financial support.

#### REFERENCES

- 1. Nahm, S.; Weinreb, S.M. Tetrahedron Lett 1981, 22, 3818
- For a review concerning Weinreb amides see Sibi, M.P. Org.Prep.Proced.Intl. 1993, 25, 15.
- 3. Aidhen, I.S.; Ahuja, J.R. Tetrahedron Lett. 1992, 33, 5431.
- 4. Shimizu, T.; Osako, K.; Nakata, T. Tetrahedron Lett. 1997, 38, 2685.
- 5. Handa, S.; Gibson, C.L. Tetrahedron Assymmetry. 1996, 7, 1281.
- Deng, J.; Hamada, Y.; Shioiri, T.; Matsunaga, S.; Fusetani, M. Angew. Chem. Int. Engl. 1994, 33, 1729.
- 7. Brenner-Weiß, G.; Giannis, A.; Sandhoff, K. Tetrahedron. 1992, 48, 5855.
- 8. Wernic, D.; DiMaio, J.; Adams, J. J. Org. Chem. 1989, 54, 4224.
- 9. Ley, S.V.; Meek, G.; Metten, K.H.; Pique, C.; J. Chem. Soc., Chem. Commun, 1994, 1931.
- 10. Goel, O.P.; Krolls, U.; Stier, M.; Kesten, S., Org. Synth. 1989, 67, 69.
- 11. Einhorn, J.; Einhorn, C.; Luche, J-L. Synth. Commun. 1990, 20, 1105.
- Sibi, M.P.; Stessman, C.C.; Schultz, J.A.; Christensen, J. W.; Lu, J.; Marvin, M. Synth. Commun, 1995, 25, 1255.
- 13. Mann, A.; Aniello, F.D. J. Org. Chem. 1996, 61, 4870.
- 14. Roux, F; Mangras, I; Poncet, J; Patrick J et G.N, Tetrahedron. 1994, 50, 5345.
- 15. Irako, N; Hamada, Y; Shiori, T. Tetrahedron. 1992, 48, 7251.

ACCEPTED 01/20/99