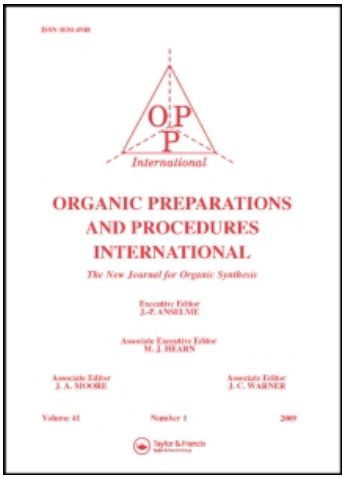

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IMPROVED SYNTHESIS OF PHENYLACETAMIDES BY THE WILLGERODT REACTION WITH MICROWAVE HEATING

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REFERENCES

1. J. March, *Advanced Organic Chemistry*, 4th Ed., John Wiley & Sons, New York, 540 (**1992**).

2. S. Budavari, Editor, *The Merck Index*, 11th Ed., Merck & Co., Inc., Rahway, N.J., 621 (**1989**).

3. a) M. Sittig, *Pharmaceutical Manufacturing Encyclopedia*, 2nd Ed. Noyes Publications, Park Ridge, New Jersey, 622 (**1988**); b) A.S. Tomcufcik, R.G. Child and A.E. Sloboda; U.S. Patent 3,784,701 (1974); c) D.H. Hey and R. Wilkinson, *J. Chem Soc.*, 1030 (**1940**).

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IMPROVED SYNTHESIS OF PHENYLACETAMIDES BY THE WILLGERODT REACTION WITH MICROWAVE HEATING

Submitted by (12/21/94) Christopher R. Strauss* and Robert W. Trainor

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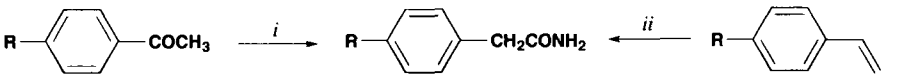
The Willgerodt reaction typically involves heating alkyl aryl ketones with sulfur and aqueous ammonia in a closed system to form terminal amides with the same number of carbon atoms.[1,2] Reaction times of several hours are common and high pressures result from H_2S formation. During lengthy reactions, appreciable amounts of the amide can be hydrolyzed to the corresponding



1

a) R = H b) R = OH
c) R = OAc d) R = OMe
e) R = OEt

2

a) R = H b) R = OH
c) R = OMe d) R = OEt

1f, R = H

i) S_8, aq. NH_3, py or *i*-PrOH, Δ *ii*) S_8, aq. NH_3, py, 2 mol % 4-(*t*-Bu)catechol, Δ

carboxylic acid,[3] thereby reducing the yield. In the Kindler modification,[4] anhydrous conditions are employed, typically with primary or secondary amines (*e.g.* morpholine), but substituted thioamides are formed except when anhydrous ammonia is used.[5] Reaction times are still in the order of hours. Thus without the inconvenience of using anhydrous ammonia, the Kindler modification is not suited to the

preparation of primary amides of carboxylic acids. In the present work, the synthesis of phenylacetamides **2a-d** from acetophenones **1a-e** and styrene[6] (**3**) *via* the Willgerodt reaction was reinvestigated.

We recently reported on a laboratory-scale microwave batch reactor (MBR) for use at elevated temperatures and pressures.[7,8] In this apparatus, a reaction carried out on the 100 mL scale at 200° for 10 min, could be completed after a total time of only 15 min, the heating up and cooling down stages each requiring *ca.* 2.5 min. The MBR thus seemed well suited for the study of the Willgerodt reaction.

The yields of phenylacetamides obtained using the MBR are shown in the table and compare favorably with those obtained previously by others using conventional heating. At comparable temperatures, however, the MBR reactions were completed within minutes, not hours (see Table), and

Table. Yields, mps, Reaction Conditions and NMR Data of Compounds **2**

Prod.	Start. Mat.	Time (min)	Temp. (°C)	mp (°C) [Lit. mp]	Yield (%)	^{1}H NMR (δ, ppm; *J*, Hz)	^{13}C NMR (δ, ppm)
2a	**1a**	10	185	157-158 [158-159][a]	72	3.37, s; 6.91, bs; 7.1-7.35, m; 7.48, bs	42.2, 126.1, 128.0, 129.0, 136.4, 172.2
2a	**3**	10	170		51[b]		
2b	**1b**	20	210	186-188 [188-189][c]	62	3.31, s; 3.74, s; 6.85, m; 7.19, m; 7.43, bs	41.3, 54.9, 113.5, 129.9, 157.8, 128.3, 172.6
2c	**1c**	20	190	176-178 [184][d]	62[e,f]	1.36, t, *J* 7.0; 3.32, s; 4.02, q, *J* 7.0; 6.88, m; 7.18, m; 7.45, bs	14.7, 41.6, 62.9, 114.1, 128.3, 130.0, 167.5, 172.6
2d	**1d**	20	210	171-173 [172-174][g]	59[h,i]	3.27, s; 6.71, m; 6.85, bs; 7.08, m; 7.39, bs; 9.26, bs	41.4, 114.9, 126.6, 129.9, 155.8, 172.8
2d[j]	**1e**	20	210		61		

a) Ref. 11 b) Reaction at 180°/10 min gave **2a** in 35% yield. c) Ref. 12 d) Ref. 13 e) Contaminated with *ca.* 5% 4'-ethoxybenzamide. f) Reactions conducted at 180°/5 min and 185°/10 min contained *ca.* 70% and 40% **1c** respectively. g) Ref. 14 h) Reactions in py instead of *i*-PrOH gave intractable gums. i) Reaction at 200°/10 min returned mainly **1d**. j) Acetoxy group was hydrolyzed in the reaction.

amide hydrolysis was negligible, thus constituting a significant improvement on established methods.[1] The convenience of the MBR, and its capabilities for both rapid heating and cooling, allowed the reaction conditions to be readily optimized. Finally, work-up procedures have been developed herein to minimize contamination of the products by sulfur.[9,10]

EXPERIMENTAL SECTION

All reactions were conducted in the MBR. ^{1}H and ^{13}C NMR spectra were recorded in d_6-DMSO at

200 and 50 MHz, respectively, and TMS was used as an internal standard. Melting points were determined on a Gallenkamp apparatus and are uncorrected. Decolorizing charcoal was employed for all recrystallizations and products were dried *in vacuo* over P_2O_5. Styrene, acetophenone, 4'-hydroxy-, 4'-methoxy- and 4'-ethoxyacetophenone were purchased from Aldrich Chemical Company. 4'-Acetoxyacetophenone was prepared from 4'-hydroxyacetophenone by treatment with Ac_2O/pyridine at ambient temperature for 48 hrs.

Phenylacetamide (2a).- A mixture of sulfur (15.0 g, 58.4 mmol), pyridine (15 mL), aq. NH_3 (28%; 20 mL) and **1a** (10.0 g, 83.3 mmol) was heated at 185° (max. pressure: 1.84 MPa) for 10 min, with stirring, and then rapidly cooled. The mixture was concentrated and the residue suspended in Et_2O (80 mL), filtered, and the solid washed with Et_2O (2 × 10 mL), suspended in boiling water (*ca.* 1 L), and filtered. The filtrate was continuously extracted with CH_2Cl_2 (500 mL) for 24 hrs and the organic phase evaporated. The residue was recrystallized from CH_2Cl_2 to afford **2a** as colorless flakes (8.1 g, 72%). When styrene (**3**; 8.7 g, 83.3 mmol) was used in place of **1a**, with the addition of 4-(*t*-Bu)catechol (0.23 g, 1.7 mmol), reaction at 170° (max. pressure: 1.66 MPa) for 10 min, afforded **2a** (5.7 g, 51%).

4'-Methoxyphenylacetamide (2b).- A mixture of sulfur (15.0 g, 58.4 mmol), *i*-PrOH (15 mL), aq. NH_3 (28%; 20 mL) and **1b** (12.5 g, 83.3 mmol) was heated at 210° for 20 min (max. pressure: 5.67 MPa), then cooled. The product mixture was concentrated and the residual semi-solid was triturated with Et_2O (3 × 30 mL). Recrystallization of the remaining solid from water afforded **2b** as colorless plates (8.5 g, 62%).

4'-Ethoxyphenylacetamide (2c).- A mixture of sulfur (15.0 g, 58.4 mmol), pyridine (15 mL), aq. NH_3 (28%; 20 mL) and **1c** (13.7 g, 83.3 mmol) was heated at 190° for 20 min (max. pressure: 2.87 MPa), then cooled. The resultant mixture was concentrated and the residual semi-solid was triturated with Et_2O (3 × 30 mL). The remaining solid was extracted with boiling water (5 × 300 mL) and filtered. The combined aqueous phase was continuously extracted with CH_2Cl_2 (500 mL) for 24 hrs. The organic phase was concentrated and the residue was recrystallized from EtOH to give **2c** (9.2 g, 62%).

4'-Hydroxyphenylacetamide (2d).- A mixture of sulfur (15.0 g, 58.4 mmol), *i*-PrOH (15 mL), aq. NH_3 (28%; 20 mL) and **1d** (11.3 g, 83.1 mmol) was heated at 210° for 20 min (max. pressure: 5.21 MPa), then rapidly cooled and concentrated. The residue was triturated with Et_2O (3 × 50 mL) and the remaining solid extracted with boiling water (1 × 500 mL, 2 × 250 mL). The combined aqueous phases were evaporated and the residue was recrystallized from water to afford **2d** as a yellow powder (7.4 g, 59%). When 4'-acetoxyacetophenone (**1e**; 14.8 g, 83.3 mmol) was reacted under the same conditions, workup afforded **2d** (7.6 g, 61%).

REFERENCES

1. E. V. Brown, *Synthesis*, 358 (**1975**).

2. R. Wegler, E. Kühle and W. Schäfer in: *"Newer Methods of Preparative Organic Chemistry,"* Vol. III, p.1, W. Foerst, ed., Academic Press, New York, NY, 1964.

3. D. F. DeTar and M. Carmack, *J. Am. Chem. Soc.*, **68**, 2025 (1946).

4. K. Kindler, *Ann.*, **431**, 187 (1923).

5. G. N. Mott, US Patent 5041657; *Chem Abstr.*, **115**: P 182861e (1991).

6. J. H. King and F. H. McMillan, *J. Am. Chem. Soc.*, **68**, 525 (1946).

7. K. D. Raner, C. R. Strauss, J. S. Thorn and R. W. Trainor, *J. Org. Chem.*, **60**, 2456 (1995).

8. A patent application has been filed.

9. E. R. Shepard, H. D. Porter, John F. Noth and C. K. Simmans, *J. Org. Chem.*, **17**, 568 (1952).

10. E. Mosettig and J. van de Kamp, *J. Am. Chem. Soc.*, **55**, 3442 (1933).

11. C. H. Davis and M. Carmack, *J. Org. Chem.*, **12**, 76 (1947).

12. A. Burger and S. Avakian, *ibid.*, **5**, 606 (1940).

13. A. Werner, *Ann.*, **322**, 151 (1902).

14. A. C. Ott, L. A. Mattano and G. H. Coleman, *J. Am. Chem. Soc.*, **68**, 2633 (1946).

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A CHEMOENZYMATIC SYNTHESIS OF (R)-2-(1-HYDROXYETHYL)-1,3-DITHIANE

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Enantiomerically pure hydroxyalkyl-1,3-dithianes are versatile bifunctional building blocks for the preparation of chiral natural products and drugs.[1-5] The hydroxyl group can be converted to other functional groups by activation and substitution, while the dithiane group can be deprotonated and then treated with electrophiles. Subsequent hydrolysis or reductive desulfurization offers an access to hydroxyketones and alcohols respectively. It is also possible to hydrolyze hydroxyalkyldithianes to yield hydroxyaldehydes.[6,7] This paper reports a new, inexpensive one-step preparation of 2-acetyl-1,3-dithiane (**2**) and the first microbiological preparation of (R)-2-(1-hydroxyethyl)-1,3-dithiane ((**R**)-**4**)[2,8] by reduction of ketone **2**.