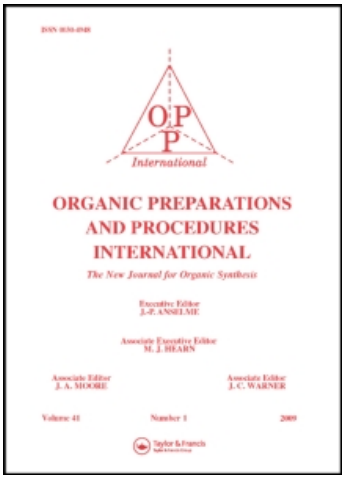

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AN IMPROVED SYNTHESIS OF FENBUFEN

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AN IMPROVED SYNTHESIS OF FENBUFEN

Submitted by (11/14/94)

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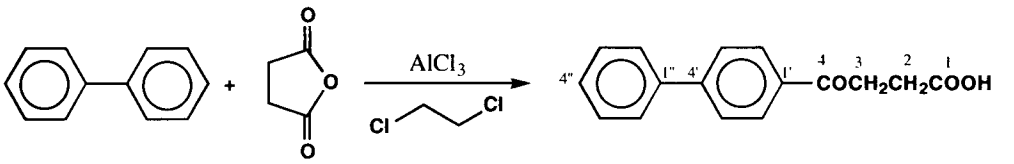
Nitrobenzene is a very useful solvent in Friedel-Crafts acylations.[1] Some advantages of this solvent are: its inertness, its high polarity which facilitates the dissolution of the usual catalyst $AlCl_3$ to form a homogeneous reaction medium, and its ability to form a bulky complex with $AlCl_3$-acylating reagent which these leading to the formation of regiospecific products from substitution in the less sterically hindered positions of the substrate. However, nitrobenzene is not always an ideal solvent, since it is toxic and its recovery requires a steam distillation at the end of the reaction. Clearly then, in those Friedel-Crafts acylation reactions where orientation of the acyl group is not a problem, it is preferable to use a solvent which is easier to recover. This paper reports a simple and a convenient synthesis of the antiinflammatory agent *fenbufen*, (3-(4-biphenylcarbonyl)propionic acid).[2] This drug has been synthesized from biphenyl and succinic anhydride using nitrobenzene as solvent and $AlCl_3$ as catalyst, a process that takes from four to six days.[3]



If we assume that biphenyl has the 2,6- and 2´,6´-positions sterically hindered, we can expect that only the equivalent positions 4 and 4´ will be available for substitution.Thus, nitrobenzene is not needed in this reaction. Therefore, a solvent with a lower boiling point, e. g., as 1,2-

dicholoroethane, can be used instead. Considering the inconvenience in time and cost for an industrial process using nitrobenzene, we studied the synthesis of fenbufen using 1,2-dicholoroethane as solvent, and the influence of succinic anhydride and $AlCl_3$ concentrations on the time and yield of the product. The amount of solvent recovered in this reaction was also determined.

Table 1 indicates that the reaction was completed in 90 min using an excess of succinic anhydride and $AlCl_3$, with a solvent recovery of up to a 92%. The yield of crude fenbufen was very high (97%) and the product was easily purified. Its identity was established by its melting point, IR, ^1H NMR, ^{13}C NMR and Mass Spectral data.

Table 1. Synthesis of Fenbufen using 1,2-Dichoroethane[a]

Reaction	Biphenyl g(mmol)	Succinic anhydride g (mmol)	$AlCl_3$ g(mmol)	Yield (%)	1,2-Dichoroethane (mL) used	recovered
1	4.3 (27.9)	3.4 (34.0)	21.6 (162.0)	83	17.81	12.83
2	6.0 (38.9)	5.5 (55.0)	13.1 (98.2)	91	24.56	22.00
3	10.0 (64.8)	7.78 (77.7)	17.3 (129.7)	81	32.42	25
4	10.0 (64.8)	7.78 (77.7)	20.73 (155.5)	97	32.42	30

a) See experimental part for details. In all cases the reaction time was 90 min.

EXPERIMENTAL SECTION

Chemicals were obtained from Aldrich. The melting points were determined on a Büchi 530 apparatus and are uncorrected. Reactions were monitored by TLC using silica gel plates 60 F_{254} (Merck, Art. 5729) eluted with Toluene - THF - 6M CH_3COOH (180:18:6). The IR spectrum was recorded on a Perkin Elmer 337 grating spectrometer as KBr palettes, signals are in cm^{-1}. The ^1H NMR and ^{13}C NMR spectra were run on a Varian VXR- 300s spectrometer in DMSO-d_6 solution using TMS as internal standard; signals are in d(ppm). The mass spectrum was determined on a Hewlett-Packard 5988 GC-mass spectrometer.

3-(4-Biphenylcarbonyl)propionic acid (fenbufen).- A stirred mixture of 20.73 g (155.5 mmol) of anhydrous $AlCl_3$ and 32.42 mL of 1,2-dichloroethane was treated at 5-10° with an intimate powdered mixture of 10 g (64.8 mmol) of biphenyl and 7.78g (77.7 mmol) of succinic anhydride. After 90 min. of stirring at 10-15°, the mixture was carefully treated with HCl 30% (50 mL) and water (150 mL). The solvent was removed by distillation; 30 mL was recovered. The remaining reaction mixture was filtered and the pale brown residue air dried to give 16 g (97%) of crude fenbufen, mp. 182-183°. The crude product was dissolved in 1500 mL of hot 1N Na_2CO_3, and the insoluble impurities were separated by filtration. The clear filtrate was treated with conc. HCl to pH ~ 6. The precipitated product (15 g, 91%), mp. 183-184°, was collected while still warm and then washed with water to pH ~ 7. A 1-g sample of the dried product was recrystallized from methanol giving white crystals, mp. 184-185°, lit.[2] 185-187°. IR (KBr): 3032, 2920, 2760, 2666, 2584, 1710, 1670 cm^{-1}. ^1H NMR: δ 2.62 (t, J = 16 Hz, 2H, $C\underline{H}_2COOH$), 3.29 (t, J = 16. Hz, 2H, $C\underline{H}_2COAr$), 7.2 - 8.08 (m, 9H, Ar-H). ^{13}C NMR: δ 27.89, 33.13, 127, 17.1, 128.2, 128.4, 128.6, 135.3, 139, 144.6, 174, 198. MS *m/e* : 254 (M^+, 10), 181 (100), 152 (39).

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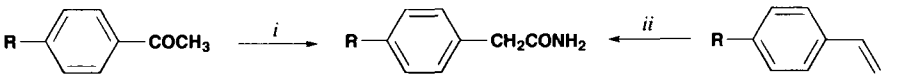
The Willgerodt reaction typically involves heating alkyl aryl ketones with sulfur and aqueous ammonia in a closed system to form terminal amides with the same number of carbon atoms.[1,2] Reaction times of several hours are common and high pressures result from H_2S formation. During lengthy reactions,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