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for the Preparation
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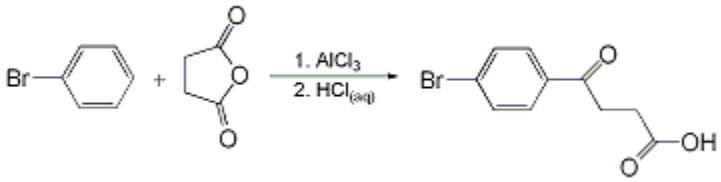
September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.079.0204

Organic Syntheses, Coll. Vol. 10, p.125 (2004); Vol. 79, p.204 (2002).

3-(4-BROMOBENZOYL)PROPANOIC ACID

[Bromobutanoic acid, 4-bromo-γ-oxo-]



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Checked by Ayako Ono and Koichi Narasaka.

1. Procedure

A 500-mL, three-necked, round-bottomed flask (Note 1) equipped with an overhead mechanical stirrer, is charged with powdered succinic anhydride (10.01 g, 0.1000 mol) (Note 2) and bromobenzene (96.87 g, 0.6170 mol) (Note 2) under dry argon. The resulting white mixture is cooled to 0°C before anhydrous aluminum chloride (26.67 g, 0.2000 mol) (Note 2) is added in one portion (Note 3). The reaction conditions are maintained over a period of 4 hr before the reaction mixture is allowed to warm to room temperature. The reaction mixture is stirred for 96 hr at room temperature (completion of the reaction is indicated by cessation of the evolution of hydrogen chloride gas) and is then poured into cooled (0°C), mechanically stirred hydrochloric acid (250 mL, 37%) (Note 4) and stirred for 1 hr. The white precipitate is filtered off, washed well with water (1 L) and dried overnight on a Büchner funnel. The crude product (24.81 g, 97%) is crystallized from dry toluene (Note 5) and dried under reduced pressure (P_2O_5, $CaCl_2$, 18 hr) to afford a white crystalline product (first fraction, 20.76 g, second fraction, 3.47 g); yield is 24.23 g (94%) (Note 6).

2. Notes

1. The glassware was dried in an oven at 130°C, assembled while still hot, and alternately evacuated and flushed with argon.
2. The checkers purchased succinic anhydride, bromobenzene and aluminum chloride from Wako Pure Chemical Industries, Ltd, Tokyo Chemical Industry Co., and Kanto Chemical Co. respectively, and used them as received.
3. Upon the addition of the aluminum chloride the reaction progressively turned from a yellow suspension to a clear yellow to a clear orange-red solution.
4. The checkers used 35-37% hydrochloric acid (340 mL) purchased from Kokusan Chemial Works, Ltd.
5. The toluene was dried over sodium metal.
6. The product showed the following physical and spectroscopic characteristics: mp 147-148°C (lit.[2] 149.5-150.2°C). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.59 (2 H, t, ^3J = 6.5), 3.21 (2 H, t, ^3J = 6.5), 7.88 (2 H, d, ^3J = 8.8), 7.96 (2 H, d, ^3J = 8.8), 12.19 (1 H, s) ; ^{13}C NMR (126 MHz, DMSO-d_6) δ: 28.3, 33.6, 127.7, 130.3, 132.2, 135.9, 174.1, 198.2; IR (KBr) cm^{-1}: 3400-2600, 1730, 1670, 1585, 1479, 1447, 1410, 1332, 1281, 1241, 1198, 1105, 1074, 990, 905, 840, 791. MS m/z 256.2(M+), 185.1, 183.1 (100%), 157.1, 155.1, 76.1, 75.1. Anal. Calcd for $C_{10}H_9BrO_3$: C, 46.72; H, 3.53. Found: C, 46.69; H, 3.49.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995

3. Discussion

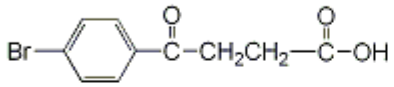
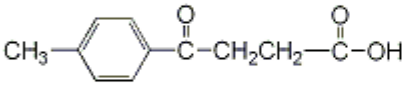
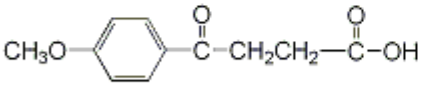
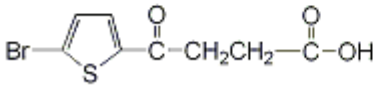
Recently we have reported the first highly efficient synthesis of ferroelectric liquid crystals bearing the 2-alkoxythiophene unit via Lawesson's reagent-mediated cyclization of γ-keto esters.[3] [4] The requisite γ-keto acids were initially targeted through acylation of appropriately substituted aryl compounds using the procedure described by Fieser et al.[5] A literature search reveals that acylation of aryl units with succinic anhydride is almost always carried out using this procedure which requires elevated temperatures. Recent studies have shown that the acylation of bromophenyl systems using this procedure results in problematic debromination[2] and considerably lower yields.[6] In repeating the method of Fieser it was found that acylation of bromobenzene gave lower yields and a substantial quantity (8% by ^{1}H NMR) of the ortho product as well as the desired para isomer.

Our improved methodology uses low temperatures and extended reaction times, and has been shown to give consistently high yields of purified materials combined with complete regioselectivity in a variety of aryl systems (see Table I). The procedure is the first reliable, simple and general method for acylation of aryl systems using succinic anhydride . In addition, it was noted that the reaction conditions also gave the highest reported yield (previous yields range from 55-63% [7]) for acylation of bromothiophene with succinic anhydride. Of particular interest was the fact that we did not observe any ring opening that is so often reported in reactions involving combinations of aluminum chloride and thiophene derivatives.[8]

The methodology may also be applicable to the synthesis of pharmacodynamic agents based on the alkoxythiophene core.[9] Such materials should be readily accessible via our new cyclization methodology[3], [4], [10] which utilizes the γ-keto acid precursors.

TABLE I

FRIEDEL-CRAFTS ACYLATION OF AROMATIC COMPOUNDS USING SUCCINIC ANHYDRIDE

Product	Reaction Time	Purified Yield (%)
	96 hr	94
	216 hr	85
	120 hr	98
	5 hr[a]	95

[a]Nitrobenzene was used as solvent (20 mL per 1.0 g of bromothiophene) and the reaction mixture was held at 0°C to -5°C for the entire period.

References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

3-(4-Bromobenzoyl)propanoic acid :
Benzenebutanoic acid, 4-bromo-γ-oxo- (9); (6340-79-0).

Succinic anhydride (8):
2,5-Furandione, dihydro- (9); (108-30-5).

Bromobenzene:
Benzene, bromo- (8,9); (108-86-1).

Aluminum chloride (8,9); (7446-70-0).

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