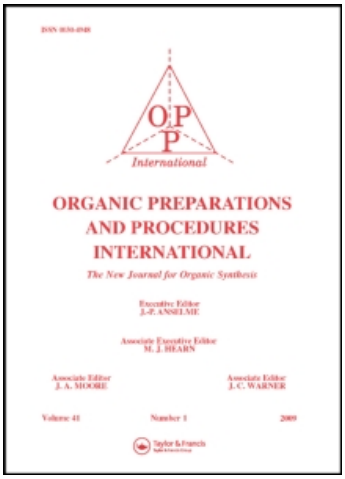

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ONE-POT REDUCTIVE DICHLOROCARBENE ADDITION TO ARYL KETONES. A NEW GENERAL METHOD FOR THE SYNTHESIS OF 2-ARYLPROPIONIC ACIDS

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OPPI BRIEFS

ONE-POT REDUCTIVE DICHLOROCARBENE ADDITION TO ARYL KETONES. A NEW GENERAL METHOD FOR THE SYNTHESIS OF 2-ARYLPROPIONIC ACIDS

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The large number of methods reported to prepare 2-arylpropionic acids is a reflection of the importance of these derivatives as non-steroidal anti-inflammatory drugs.[1] Most of the syntheses of these compounds start from aryl ketones, which can be obtained in high yield by selective electrophilic acylation. The aryl ketones can then be converted by many different routes into 2-arylpropionic acids.[2] Although a considerable amount of information about the reactivity and selectivity of carbenes is now available, the main body of this knowledge has been obtained from olefinic addition reactions. However, the addition of carbenes to the carbon-heteroatom double bonds has not been extensively investigated.[3] In an effort to simplify these syntheses, we now report the addition of dichlorocarbene to aromatic carbonyl compounds under reductive conditions in a one-pot reaction. This route provides a simple preparation of 2-arylpropionic acids, some of which like Ibuprofen and Naproxen, have already been extensively used in medical practice.

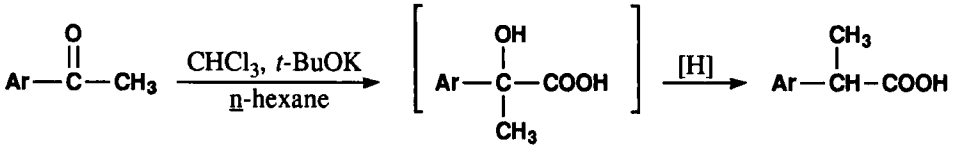
The reactions were generally performed under phase-transfer catalysis in aqueous conditions. However, the use of a modified Doering procedure[4] for the generation dichlorocarbene in a one-phase system (*n*-hexane) makes it unnecessary to isolate the hydroxy acid intermediates, as these compounds can be hydrogenolyzed *in situ* to the corresponding 2-arylpropionic acids in high yields. Treatment of a series of representative substrates with $CHCl_3$-*t*-C_4H_9OK in hexane provided the results reported in Table 1.The reduction process was carried out by hydrogenolysis (H_2, Pd/C, Method A) or by catalytic transfer hydrogenation (HCO_2H, Pd/C, Method B). Although the hydroxy acid intermediates are hydrogenolyzed very slowly under neutral conditions, it is possible to obtain good yields of the propionic acids in an acid medium ($HClO_4$, formic acid).

As shown in Table 1, satisfactory yields of arylpropionic acids were obtained, independent of the carbonyl compounds or the reduction method used. The yields obtained through Methods A and B are higher than those obtained by the Kindler modification of the Willgerodt reaction.[7] Finally, the fact that the 2-arylpropionic acids have acquired importance as anti-inflammatory agents, may make this inexpensive method worthwhile in certain cases.

TABLE 1. Yields and mp of Arylpropionic Acids[a]

Cmpd	Yield (%)		mp[b] (°C)
	Method A	Method B	
3a	65	60	160 [c,d]
3b	50	55	70-72 [d]
3c	50	40	57 [d]
3d	45	55	92 [d]
3e	40	45	70-71 [d]
3f	40	40	75-77 [e]
3g	55[f]	50	152-154 [f]

a) All products were obtained as racemic mixtures. b) All these compounds are known products and their mps. agreed with those recorded in literature. c) bp. at 25 mm d) lit. ref.[5] e) lit. ref.[6] f) lit. ref. [7]; the Willgerodt-Kindler reaction gave a 29% yield of this compound.



1 **2** **3**

a) Ar = C_6H_5, b) Ar = *p*-MeC_6H_4, c) Ar = *p*-$MeOC_6H_4$, d) Ar = *p*-ClC_6H_4
e) Ar = *p*-*iso*-$C_3H_7C_6H_4$, f) Ar = *p*-*iso*-$C_4H_9C_6H_4$ g) Ar = 6-methoxy-2-naphthyl

EXPERIMENTAL SECTION

The starting ketones were obtained from Aldrich Chem. or were prepared according to the methods described in the literature [8].

Preparation of 2-(6-Methoxy-2-naphthyl)propionic Acid. Typical Procedure.- A stirred mixture of 6-methoxy-2-acetylnaphthalene (1 g, 5 mmol)[8] and potassium *t*-butoxide (0.56 g, 5 mmol) in dry *n*-hexane (10 mL), was cooled in an ice bath at 0°, was added dropwise dry chloroform (0.59 g, 5 mmol); the reaction mixture was stirred for 30 min at room temperature. The reduction step then was carried out by either of the methods below.

Method A (Using H_2, Pd/C).- To the above solution perchloric acid (0.5 mL) and 10% Pd/C (50 mg) were added. The reaction was hydrogenated at room temperature until hydrogen uptake stopped. The catalyst was removed by filtration. The organic layer was diluted with water and extracted with Et_2O. The ethereal phase was dried and evaporated *in vacuo* to yield the crude acid. Flash column chromatography (SiO_2, dichloromethane:*n*-hexane 9:1, v/v)[9] gave 2-(6-methoxy-2-naphthyl)propionic acid (0.63 g, 55%), mp. 152°, lit.[5] mp. 150-151°.

Method B (HCO_2H).- To the above solution, 85% formic acid (5 mL, 0.13 mol) was added. The reaction was stirred with 10% Pd/C (50 mg) at room temperature for 6 hrs. The catalyst was filtered off and the filtrate was diluted with water. The product was worked up as above to give a 50% yield.

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