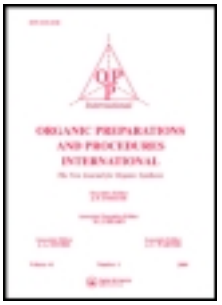

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IMPROVED PREPARATION OF FLURBIPROFEN

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IMPROVED PREPARATION OF FLURBIPROFEN†

Submitted by M. N. Deshmukh* and V. Lakshminarayana
(10/30/97)

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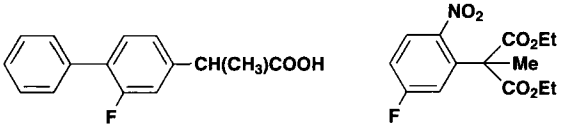
Diethyl 2-methyl-2-(3-fluoro-4-nitrophenyl)malonate (**4**) is an important intermediate for the manufacture of the non-steroidal anti-inflammatory drug, flurbiprofen (**1**). The reported methods for its synthesis involve arylation of diethyl methylmalonate (**2**) with 2,4-difluoronitrobenzene (**3**) using a strong base such as sodium hydride in DMSO (57%),[1] sodium hydroxide or K_2CO_3 in DMF at

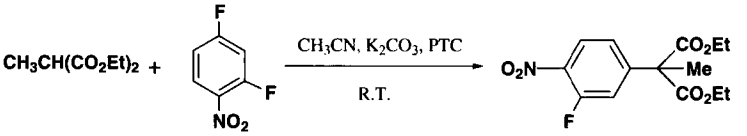


1 **5**

30-160° (51-80%).[2] The arylation was also carried out in DMF using K_2CO_3 and traces of 18-crown-6,[2c] albeit leading to a mixture of *ortho* (**5**) and *para* (**4**) products. Further the reaction times are longer

and associated with low yield of the desired product. Thus, it became necessary to develop a convenient method for the synthesis of **4**.

We report herein the synthesis of the intermediate **4** using phase-transfer catalysts (PTC), which provides the desired *para* isomer **4** as a major product. Alkylation of **2** with **3** in dry acetonitrile in presence of different PTCs has been investigated and the results are summarized in the table.



3 **4**

Table. Alkylation of **2** with **3** using PTCs[a]

Entry	PTC Used	Temp. (°C)	Time (h)	Yield (%)[b]	*o/p* ratio
1	$BnEt_3N^+Cl^-$	RT	24	86	6/94
2	$BnEt_3N^+Cl^-$	55	16	80	6/94
3	$Bu_4N^+Cl^-$	RT	72	15	6/94
4	$Bu_4N^+Br^-$	RT	72	32	7/93
5	$Et_4N^+Cl^-$	RT	24	83	6/94
6	$Bu_4N^+I^-$	RT	72	–	–

a) All the reactions were conducted using 10 mmol of **2** and 10 mmol of **3**. b) Yields refer to the isolated yield. The ratio of *o/p* isomers was determined by GC.

In summary, the present study provides a convenient method for the synthesis of flurbiprofen intermediate **4** under mild conditions using easily accessible PTCs.

EXPERIMENTAL SECTION

^1H NMR spectra were recorded on Varian 200 MHz with TMS as internal standard. Acetonitrile was dried over P_2O_5. K_2CO_3 (18-30 mesh) was dried at 100° for 3 h and immediately used for the reaction.

Diethyl 2-Methyl-2-(3-fluoro-4-nitrophenyl)malonate (4).- A mixture of 2,4-difluoronitrobenzene (50 g, 0.314 mol), diethylmethylmalonate (55.68 g, 0.32 mol), K_2CO_3 (65 g, 0.471 mol) and benzyltriethylammonium chloride (7.127 g, 0.031 mol) were stirred in dry acetonitrile (500 mL) under nitrogen atmosphere at 55° for 16 h. The reaction was monitored by GC. Acetonitrile was removed under vacuum, water (300 mL) was added to the residue and extracted with ethyl acetate (3 x 200 mL). The organic layer was washed with water followed by a brine solution and dried over Na_2SO_4. The organic layer was concentrated. Vacuum distillation of the crude product (180°/0.1 mm) yielded 73 g (74%) of the title compound as a pale yellow liquid (*ortho:para* 6:94). ^1H NMR ($CDCl_3$): δ 8.06 (t, J = 8.2 Hz, 1H), 7.24-7.39 (m, 2 H), 4.24 (q, $J_{1,2}$ = 8 Hz, $J_{1,3}$ = 12 Hz, 4 H), 1.82 (s, 3 H), 1.3 (t, J = 6 Hz, 6 H).

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EFFICIENCY OF THE VILSMEIER-HAACK METHOD IN THE SYNTHESIS OF *p*-AMINOBENZALDEHYDES

Submitted by (09/29/97)

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Aromatic aldehydes[1] and their oximes[2] are important synthetic intermediates. In addition, *p*-aminobenzaldoximes show interesting chemical and biological activities.[3] It is known that only thermodynamically more stable *E*-oximes are formed by direct oximation of aromatic aldehydes,[4] thus, the product of reaction of *p*-(N,N-dimethylamino)benzaldehyde with hydroxylamine[5] is *E*-*p*-(N,N-dimethylamino)benzaldoxime[6] and it is noteworthy that *Z*-isomers of *p*-aminobenzaldoximes are not known.

Various methods are used to synthesize *p*-aminobenzaldehydes. The unstable parent *p*-aminobenzaldehyde has been obtained by the McFadyen-Stevens reaction of N'-benzenesulfonyl-*p*-amino-benzhydrazide,[7] by reduction of *p*-nitrobenzaldehyde[8] or from *p*-nitrotoluene.[9] N-Alkyl substituted *p*-formylanilines have been prepared by amination-dehalogenation of *p*-(formyl)halobenzenes,[10-12] by formylation of anilines,[13-15] from the reaction of formaldehyde with 4,4'-di(alkylamino)-N-benzylideneanilines[16] or *p*-(alkylamino)phenylmagnesium halide with alkyl formates.[17] A literature search for preparative procedures shows that the Vilsmeier-Haack and Duff[18] methods were most commonly used. The present paper describes the efficiency of formylation of various anilines by the