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## Organic Preparations and Procedures International: The New Journal for Organic Synthesis

Publication details, including instructions for authors and subscription information:

<http://www.tandfonline.com/loi/uopp20>

### IMPROVED PREPARATION OF FLURBIPROFEN

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Published online: 09 Feb 2009.

To cite this article: M. N. Deshmukh & V. Lakshminarayana (1998) IMPROVED PREPARATION OF FLURBIPROFEN, Organic Preparations and Procedures International: The New Journal for Organic Synthesis, 30:4, 453-455, DOI: [10.1080/00304949809355309](https://doi.org/10.1080/00304949809355309)

To link to this article: <http://dx.doi.org/10.1080/00304949809355309>

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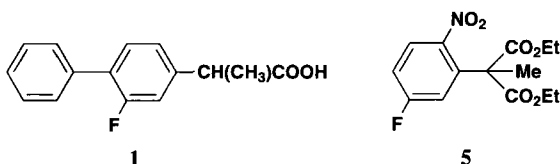
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### IMPROVED PREPARATION OF FLURBIPROFEN<sup>†</sup>

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

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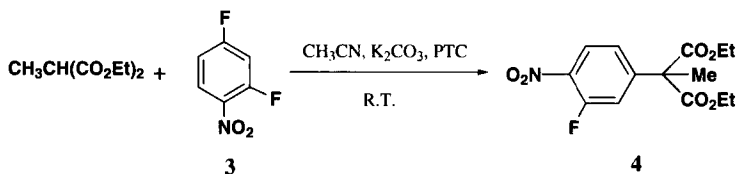
Diethyl 2-methyl-2-(3-fluoro-4-nitrophenyl)malonate (**4**) is an important intermediate for the manufacture of the non-steroidal anti-inflammatory drug, flurbiprofen (**1**). The reported methods for its synthesis involve arylation of diethyl methylmalonate (**2**) with 2,4-difluoronitrobenzene (**3**)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



30-160° (51-80%).<sup>2</sup> The arylation was also carried out in DMF using K<sub>2</sub>CO<sub>3</sub> and traces of 18-crown-6,<sup>2c</sup> 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.



**Table.** Alkylation of **2** with **3** using PTCs<sup>a</sup>

Entry	PTC Used	Temp. (°C)	Time (h)	Yield (%) <sup>b</sup>	<i>o/p</i> ratio
1	BnEt <sub>3</sub> N <sup>+</sup> Cl <sup>-</sup>	RT	24	86	6/94
2	BnEt <sub>3</sub> N <sup>+</sup> Cl <sup>-</sup>	55	16	80	6/94
3	Bu <sub>4</sub> N <sup>+</sup> Cl <sup>-</sup>	RT	72	15	6/94
4	Bu <sub>4</sub> N <sup>+</sup> Br <sup>-</sup>	RT	72	32	7/93
5	Et <sub>4</sub> N <sup>+</sup> Cl <sup>-</sup>	RT	24	83	6/94
6	Bu <sub>4</sub> N <sup>+</sup> I <sup>-</sup>	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

<sup>1</sup>H NMR spectra were recorded on Varian 200 MHz with TMS as internal standard. Acetonitrile was dried over P<sub>2</sub>O<sub>5</sub>. K<sub>2</sub>CO<sub>3</sub> (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<sub>2</sub>CO<sub>3</sub> (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<sub>2</sub>SO<sub>4</sub>. 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). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.06 (t, J = 8.2 Hz, 1H), 7.24–7.39 (m, 2 H), 4.24 (q, J<sub>1,2</sub> = 8 Hz, J<sub>1,3</sub> = 12 Hz, 4 H), 1.82 (s, 3 H), 1.3 (t, J = 6 Hz, 6 H).

**Acknowledgements.**— VLN thanks CSIR, New Delhi for financial assistance in the form of fellowship.

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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<sup>1</sup> and their oximes<sup>2</sup> are important synthetic intermediates. In addition, *p*-aminobenzaldoximes show interesting chemical and biological activities.<sup>3</sup> It is known that only thermodynamically more stable *E*-oximes are formed by direct oximation of aromatic aldehydes,<sup>4</sup> thus, the product of reaction of *p*-(*N,N*-dimethylamino)benzaldehyde with hydroxylamine<sup>5</sup> is *E-p*-(*N,N*-dimethylamino)benzaldoxime<sup>6</sup> 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,<sup>7</sup> by reduction of *p*-nitrobenzaldehyde<sup>8</sup> or from *p*-nitrotoluene.<sup>9</sup> *N*-Alkyl substituted *p*-formylanilines have been prepared by amination-dehalogenation of *p*-(formyl)halobenzenes,<sup>10-12</sup> by formylation of anilines,<sup>13-15</sup> from the reaction of formaldehyde with 4,4'-di(alkylamino)-*N*-benzylideneanilines<sup>16</sup> or *p*-(alkylamino)phenylmagnesium halide with alkyl formates.<sup>17</sup> A literature search for preparative procedures shows that the Vilsmeier-Haack and Duff<sup>18</sup> methods were most commonly used. The present paper describes the efficiency of formylation of various anilines by the