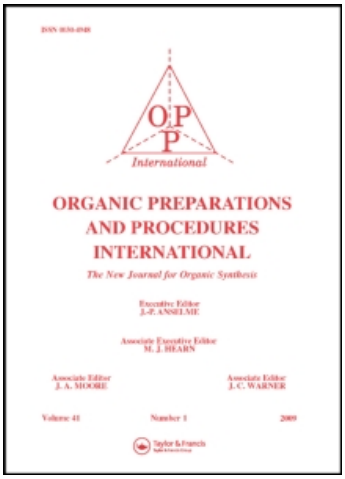

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

A CONVENIENT PREPARATION OF MONOAROYLPIPERAZINE HYDROCHLORIDES

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To cite this Article Dhawan, Balram and Southwick, Philip L.(1975) 'A CONVENIENT PREPARATION OF MONOAROYLPIPERAZINE HYDROCHLORIDES', Organic Preparations and Procedures International, 7: 2, 85 — 88
To link to this Article: DOI: 10.1080/00304947509355576
URL: http://dx.doi.org/10.1080/00304947509355576

ORGANIC PREPARATIONS AND PROCEDURES INT. 7(2), 85-88 (1975)

A CONVENIENT PREPARATION OF MONOAROYLPIPERAZINE HYDROCHLORIDES

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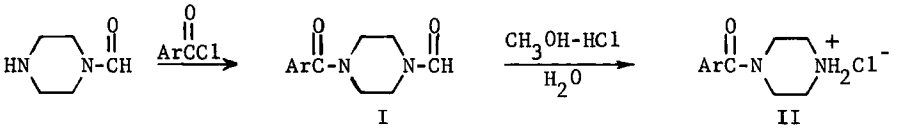
Efforts to prepare mono-aroyl derivatives of piperazine by controlled acylation of piperazine have enjoyed only limited success. Diaroyl piperazines were formed preferentially unless quite laborious procedures were used.[1,2] Other attempted methods for obtaining monoaroylpiperazines, such as selective reduction of 4-aroyl-2-piperazinones[3,4] and selective basic hydrolysis of 1-aroyl-4-carbethoxypiperazines,[1] have also proved unsatisfactory or inconvenient with respect to the starting material required. In our experience a method for obtaining monoacylpiperazines by deformylation of 1-acyl-4-formylpiperazines with sodium hydride[4,5] failed completely when applied to 1-(p-chlorobenzoyl)-4-formylpiperazine. We have found, however, that the latter compound and several other 1-aroyl-4-formylpiperazines are converted smoothly and in satisfactory yield to 1-aroylpiperazine hydrochlorides by treatment with methanolic hydrochloric acid at room temperature.[6] The reaction sequence given below therefore



I II

provides a useful synthesis of mono-aroyl derivatives of piperazine in the form of their hydrochlorides. The 1-aroyl-4-formylpiperazines (I) and 1-aroylpiperazine hydrochlorides (II) recorded in Tables I and II were obtained in the course of this work.[7] We have not tested this sequence as a route to monoalkanoylpiperazines, several of which were

obtained recently by sodium hydride deformylation of 1-alkanoyl-4-formylpiperazines.[4]

EXPERIMENTAL

4-Aroyl-1-formylpiperazines.- 1-Formylpiperazine[8] (0.1 mole) was dissolved in chloroform (200 ml) and the sodium bicarbonate (0.11 mole) was added. The mixture was stirred while the aroyl chloride (0.11 mole) in 20 ml of chloroform was added dropwise. The mixture was stirred overnight at room temperature, then extracted twice with 100 ml of water and dried (Na_2SO_4). Removal of the chloroform by use of a rotary evaporator at room temperature left the products as oils which solidified on standing. The products were obtained as crystalline white solids after recrystallization; the 4-benzoyl derivative was crystallized from benzene-n-hexane and the others from methylene chloride-petroleum ether (bp 30-60°). (See Table I.) The 4-aroyl-1-formylpiperazines showed two carbonyl absorptions at 5.9-6.0 μ and 6.1-6.2 μ. NMR spectra of all of these compounds in $CDCl_3$ solution showed the following features: δ 8.10-8.16 (singlet, 1H, -CHO); 7.34-7.46 (apparent singlet, 4 or 5H, ArH); 3.1-4.1 (multiplet, 8H, piperazine methylenes). In addition, the p-toluoyl derivative showed a singlet at δ 2.44 (3H, CH_3).

Monoaroylpiperazine Hydrochlorides.- The 4-aroyl-1-formylpiperazines (0.005 mole) were stirred at room temperature for 24 hr with 10 ml of a methanolic HCl solution prepared from 5.5 ml of conc. hydrochloric acid and 60 ml of methanol. The precipitated solids were collected by filtration and recrystallized from methanol or absolute ethanol. (See Table II.) In the case of the o-chlorobenzoyl derivatives, the crude hydrochloride did not precipitate, but was secured by taking the reaction mixture to dryness under reduced pressure in a rotary evaporator. The compounds showed a single amide carbonyl absorption at 6.0-6.2 μ. NMR spectra of all of these compounds in CDCl3/trifluoroacetic acid showed

Table I.- 4-Aroyl-1-formylpiperazines (I)

Ar	MP (°C)	Yield (%) (Crude)	Formula	Analysis[a] Calcd. (Found) C	H	N
C_6H_5	83-84	92.3	$C_{12}H_{14}N_2O_2$	66.03 (66.24)	6.47 (6.58)	12.84 (12.61)
p-ClC_6H_4	117.5-119	95.6	$C_{12}H_{13}ClN_2O_2$	57.03 (56.96)	5.15 (5.16)	11.09 (10.99)
o-ClC_6H_4	130-131	86.1	$C_{12}H_{13}ClN_2O_2$	57.03 (57.15)	5.15 (5.27)	11.09 (10.87)
p-$CH_3C_6H_4$	101-102	99.6	$C_{13}H_{16}N_2O_2$	67.24 (67.33)	6.90 (6.93)	12.07 (11.86)

a) Microanalyses are by M-H-W Laboratories, Garden City, Michigan.

Table II.- 1-Aroylpiperazine Hydrochlorides (II)

Ar	MP (°C)	Yield (%)[a]	Formula	Analysis Calcd. (Found) C	H	N
C_6H_5	274-275[b]	50	$C_{11}H_{15}ClN_2O$	58.28 (58.33)	6.62 (6.55)	12.36 (12.34)
p-ClC_6H_4	259-260	62.5	$C_{11}H_{14}Cl_2N_2O$	50.57 (50.53)	5.36 (5.40)	10.73 (10.49)
o-ClC_6H_4	244-245	53.5	$C_{11}H_{14}Cl_2N_2O$	50.57 (50.70)	5.36 (5.48)	10.73 (10.64)
p-$CH_3C_6H_4$	286-287	60.4[c]	$C_{12}H_{17}ClN_2O$	59.88 (60.00)	7.07 (7.04)	11.64 (11.60)

a) Yields are for the two-step preparation from 1-formylpiperazine; recrystallized from ethanol unless otherwise specified.
b) Lit. mp 274°; K. R. Jacobi, Ber., 66, 113 (1933).
c) Recrystallized from methanol.

the following features: δ 7.25-7.7 (apparent singlet or multiplet (o-chlorobenzoyl), 4 or 5H, ArH) 3.2-4.6 (2 broad multiplets, 8H, piperazine methylenes). In addition, the p-toluoyl derivative showed a singlet at δ 2.44 (3H, CH_3).

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(Received February 26, 1975; in revised form May 19, 1975)