A Convenient Synthesis of 1-Aryl-4-piperidones

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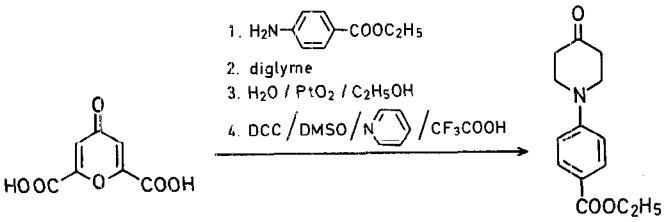
As part of an ongoing research program directed at the unequivocal synthesis of C-6, C-7 annelated methotrexate derivatives, we required an efficient synthesis of large quantities of 1-(4-ethoxycarbonylphenyl)-4-piperidone **(2a)**. This compound has been prepared[2] in 22% yield in four steps by treatment of chelidonic acid monohydrate ($1 \cdot H_2O$) with ethyl 4-aminobenzoate, followed by thermal bis-decarboxylation, catalytic hydrogenation, and oxidation.

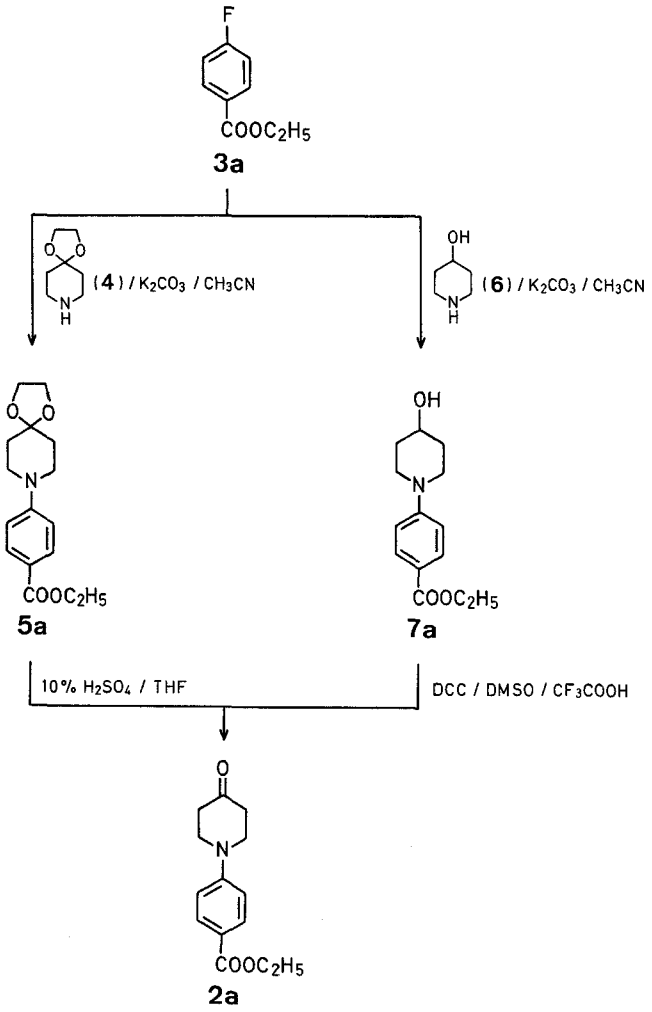


1 **2a**

0039-7881/81/0832-0606 $ 03.00

The initial step in this circuitous sequence is not suitable for convenient large scale preparation and provided inconsistent yields of the desired product in our hands. We have explored another approach to **2a** based on the work of Ref.[3], which involves the displacement of fluoride from activated aryl fluorides with appropriately functionalized piperidines. We describe in this paper a convenient synthesis of **2a** and its extension to the preparation of other substituted 1-aryl-4-piperidones **(2)**, 1-aryl-4-piperidone ethylene acetals **(5)**, and 1-aryl-4-piperidinols **(7)** with the following substituents in the 4-position of the phenyl ring: **a**, —CO—OC_2H_5; **b**, —CN; **c**, —CH=O; **d**, —CO—CH_3, and **e**, —NO_2.

Treatment of ethyl 4-fluorobenzoate **(3a)** with a stoichiometric amount of the ethylene acetal of 4-piperidone (1,4-dioxa-8-azaspiro[4,5]decane; **4**) in refluxing acetonitrile containing freshly ground anhydrous potassium carbonate for 18 h gave 1-(4-ethoxycarbonylphenyl)-4-piperidone ethylene acetal **(5a)** in 12% yield. Increasing the reaction time gave similar results, but the use of 2–3 equivalents of **4** for an extended reaction time (3–4 days) afforded **5a** in 81% yield. Mild acidic hydrolysis (10% sulfuric acid/tetrahydrofuran/3–4 days/25 °C)[4] provided **2a** in 94% yield.



Furthermore, reaction of **3a** with 4-hydroxypiperidine **(6)** furnished 1-(4-ethoxycarbonylphenyl)-4-piperidinol **(7a)**[2] in 84% yield. Treatment of **7a** with the *N,N*-dicyclohexylcarbodiimide/dimethyl sulfoxide/pyridinium trifluoroacetate reagent[2,5] in benzene at ambient temperature overnight gave **2a** in 63% yield. Extensions of these reactions to a variety of other aryl fluorides (4-cyano, 4-formyl, 4-acetyl, 4-nitro) are summarized in the Table.

This methodology provides a useful route to 1-aryl-4-piperidones not conveniently accessible by other procedures. Application of this procedure to the synthesis of 1-aryl-3-pyrrolidones and 1-aryl-3-piperidones is in progress.

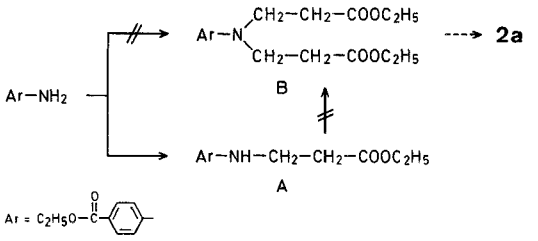
1-Phenyl-4-piperidone has been prepared by the conjugate addition of aniline to ethyl acrylate, Dieckmann condensation, and acid hydrolysis-decarboxylation[6,7], but this route is not suitable for the synthesis of **2a** because of the diminished nucleophilicity of ethyl 4-aminobenzoate[2].

Table. 1-Aryl-4-piperidone Ethylene Acetals **5**, 1-Aryl-4-piperidinols **7**, and 1-Aryl-4-piperidones **2**

Product	Substituent in 4-position of aryl ring	Yield[a] [%]	m.p. [°C] (solvent)	Molecular formula[b] or Lit. m.p. [°C][c]
5a	—CO—OC_2H_5	81	93–94.5° (benzene/hexanes)	$C_{16}H_{21}NO_4$ (291.3)
5b	—CN	82	132–133° (benzene/hexanes)	$C_{14}H_{16}N_2O_2$ (244.3)
5c	—CH=O	49	118–119° (benzene/hexanes)	$C_{14}H_{17}NO_3$ (247.3)
5d	—CO—CH_3	87	118–119° (benzene/hexanes)	$C_{15}H_{19}NO_3$ (261.3)
5e	—NO_2	91[d]	155–156° (benzene/hexanes)	$C_{13}H_{16}N_2O_4$ (264.3)
7a	—CO—OC_2H_5	84	107–108° (benzene/hexanes)	109–110°[2]
7b	—CN	81	102–103° (benzene/hexanes)	$C_{12}H_{14}N_2O$ (202.3)
7c	—CH=O	83	115–116° (isopropanol)	$C_{12}H_{15}NO_2$ (205.3)
7d	—CO—CH_3	81	123–124° (isopropanol)	127–129°[3]
7e	—NO_2	81	114–116° (isopropanol)	$C_{11}H_{14}N_2O_3$ (222.2)
2a[e]	—CO—OC_2H_5	A: 94, B: 63	59–60°	63–64.5°[2]
2b	—CN	A: 93, B: 58	98–100° (benzene/hexanes)	$C_{12}H_{12}N_2O$ (200.2)
2c	—CH=O	A: 53, B: 61	100–101° (benzene/hexanes)	$C_{12}H_{13}NO_2$ (202.2)
2d	—CO—CH_3	A: 90, B: 68	93–95° (benzene/hexanes)	$C_{13}H_{15}NO_2$ (217.3)
2e	—NO_2	A: 96, B: 79	164.5–166.5° (benzene/hexanes)	163–165°[8]

[a] Individual reaction parameters not optimized.
[b] Spectral and microanalytical data (C ±0.30, H ±0.30, N ±0.30) for all new compounds are consistent with the assigned structures.
[c] Spectral data consistent with structure and physical data with those previously reported.
[d] Reaction time 20 h.
[e] Purified by chromatography on silica gel eluting with diethyl ether.

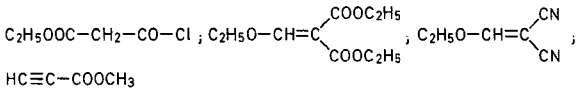
Treatment of ethyl 4-aminobenzoate with ethyl acrylate (3 equiv.) in refluxing glacial acetic acid containing a catalytic amount of copper(I) chloride (2 days) provided ethyl *N*-(4-ethoxycarbonylphenyl)-3-aminopropanoate (A) instead of the bis-adduct (B).



Reactions of A with other electrophiles gave either unreacted starting material:

$H_2C{=}CH{-}COOC_2H_5$; $HOOC{-}CH_2{-}COOC_2H_5$ / $NaBH_4$; $Br{-}CH_2{-}CH_2{-}COOC_2H_5$; $(H_3C)_3SiCl$ / $[(H_3C)_3Si]_2NH$

or complex product mixtures:



1-Aryl-4-piperidone Ethylene Acetals 5 and 1-Aryl-4-piperidinols 7; General Procedure:

A mixture of aryl fluoride **3** (0.1 mol), acetal **4** (0.2–0.3 mol) or piperidinol **6** (0.2–0.3 mol), freshly ground anhydrous potassium carbonate (0.1 mol), and acetonitrile (100 ml) is stirred under a nitrogen atmosphere at reflux for 3–4 days. The reaction mixture is allowed to cool to ambient temperature, diluted with water (100 ml), and extracted with dichloromethane (450 ml). The combined organic extracts are washed with brine (200 ml), dried with sodium sulfate, filtered, and concentrated in vacuo. Trituration with cold ethyl ether affords the product.

1-Aryl-4-piperidones 2; General Procedures:

Method A[4]: A solution of 10% sulfuric acid and tetrahydrofuran (2:1) containing acetal **5** (1 g/15 ml) is stirred at ambient temperature for 3–4 days, diluted with water (30 ml), and extracted with dichloromethane (50 ml). The combined organic extracts are washed with brine (30 ml), dried with sodium sulfate, and filtered. The solvent is removed under reduced pressure to give **2**.

Method B[2,5]: To a solution of dimethyl sulfoxide and benzene (1:2) containing piperidinol **7** (1 g/15 ml), dicyclohexylcarbodiimide (3 equiv.), and pyridine (1 equiv.), cooled in an ice-water bath under a nitrogen atmosphere, is added dropwise trifluoroacetic acid (0.5 equiv.). The reaction mixture is allowed to warm to ambient temperature overnight, diluted with ethyl acetate, and filtered. The filtrate is washed copiously with water and brine, dried with sodium sulfate, filtered, and the solvent removed in vacuo. The crude product **2** is purified as described in the Table.

Ethyl *N*-(4-Ethoxycarbonylphenyl)-3-aminopropanoate (A):

Yield: 62%; m.p. 68–69°C (from ethanol).

$C_{14}H_{19}NO_4$	calc.	C 63.38	H 7.22	N 5.28
(265.3)	found	63.12	7.48	5.21

I.R. (KBr): $\nu = 3340, 1735, 1675\ cm^{-1}$.

^1H-N.M.R. ($CDCl_3$): $\delta = 1.25$ (t, 3H, $J = 7$ Hz); 1.35 (t, 3H, $J = 7$ Hz); 2.60 (t, 2H, $J = 6.5$ Hz); 3.3–3.7 (m, 2H); 4.15 (q, 2H, $J = 7$ Hz); 4.28 (q, 2H, $J = 7$ Hz); 4.5–4.8 (m, 1H); 6.52, 7.82 ppm (AB-q, 4H, $J = 9$ Hz).

This work was supported by a grant (R01 CA28351) to Princeton University from the National Cancer Institute, National Institutes of Health.

Received: March 3, 1981

[1] Recipient of the Cyanamid Education Award, 1977–1979.

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