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An expedient synthesis of 6-arylpiperidine-2,4-diones by chain-extension of β-aryl-β-aminoacids

Nicolas Leflemme, Patrick Dallemagne* and Sylvain Rault

Centre d'Etudes et de Recherche sur le Médicament de Normandie, UFR des Sciences Pharmaceutiques, 1, rue Vaubénard, 14032 Caen cedex, France

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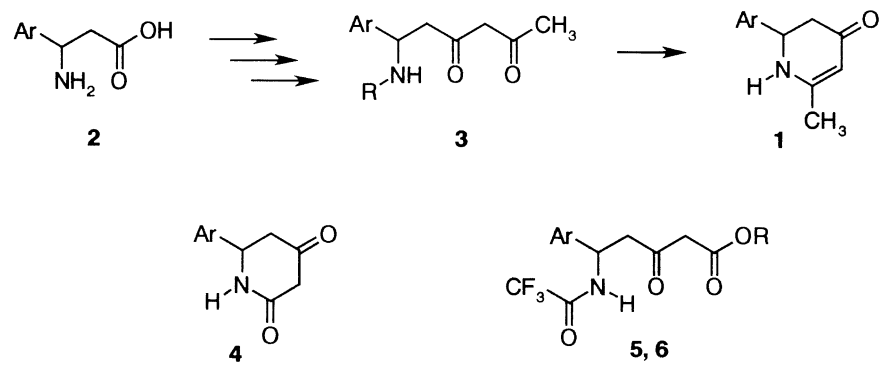
Abstract—The synthesis of novel 6-arylpiperidine-2,4-diones is described in five steps starting from β-aryl-β-aminoacids via the chain extension of the latter into δ-aryl-δ-amino-β-ketoacids. The chemical pathway involves an acylation of Meldrum's acid and yields useful building blocks for heterocyclic chemistry.

We have recently pointed out the interest of the dihydropyridones of the type **1** as memory enhancers in relation with their nicotinic acetylcholine receptor affinity.[1] Their synthesis was achieved starting from β-aryl-β-aminoacids **2**, converted in three steps into the *N*-protected δ-aryl-δ-amino-β-ketoketones **3** before being cyclised to **1** (Scheme 1).[2]

In connection with this study, we required an efficient preparation for the infrequently reported piperidinediones **4**, the oxidised analogs of **1**. Taking our experience in the β-aryl-β-aminoacids field into account, we focused on the improved synthesis of **4**, starting from these readily available, eventually chiral, starting materials.[3–6] The chemical pathway involved the cyclisation of δ-aryl-δ-amino-β-ketoacids derivatives **5**–**6**, obtained by chain-extension of **2**, rather than from the corresponding aldehydes, using Roskamp's protocol,[7] or from arylidenetoluenesulfinamides prepared in delicate conditions with expensive reagents.[8] The effectiveness of the present preparation of **4** designates furthermore **5** and **6** as useful building blocks in pseudopeptide chemistry and in some alkaloid synthesis.[9]

We chose to exploit the condensation of 3-trifluoroacetylamino-3-arylpropionyl chlorides **7a**–**d**, derived from aminothienyl, furyl and phenylpropionic acids **2a**–**d**, with Meldrum's acid in dichloromethane in the presence of pyridine, followed by refluxing in methanol or *tert* butanol, to afford the corresponding δ-aryl-δ-trifluoroacetylamino-β-ketoesters **5a**–**d** and **6a**–**d** (Scheme 2).



Scheme 1.

Keywords: 6-arylpiperidine-2,4-diones; δ-aryl-δ-amino-β-ketoacids; β-aryl-β-aminoacids; Meldrum's acid; chain-extension.
* Corresponding author. Tel.: 33 2 31 56 59 10; fax: 33 2 31 93 11 88; e-mail: dallemagne@pharmacie.unicaen.fr

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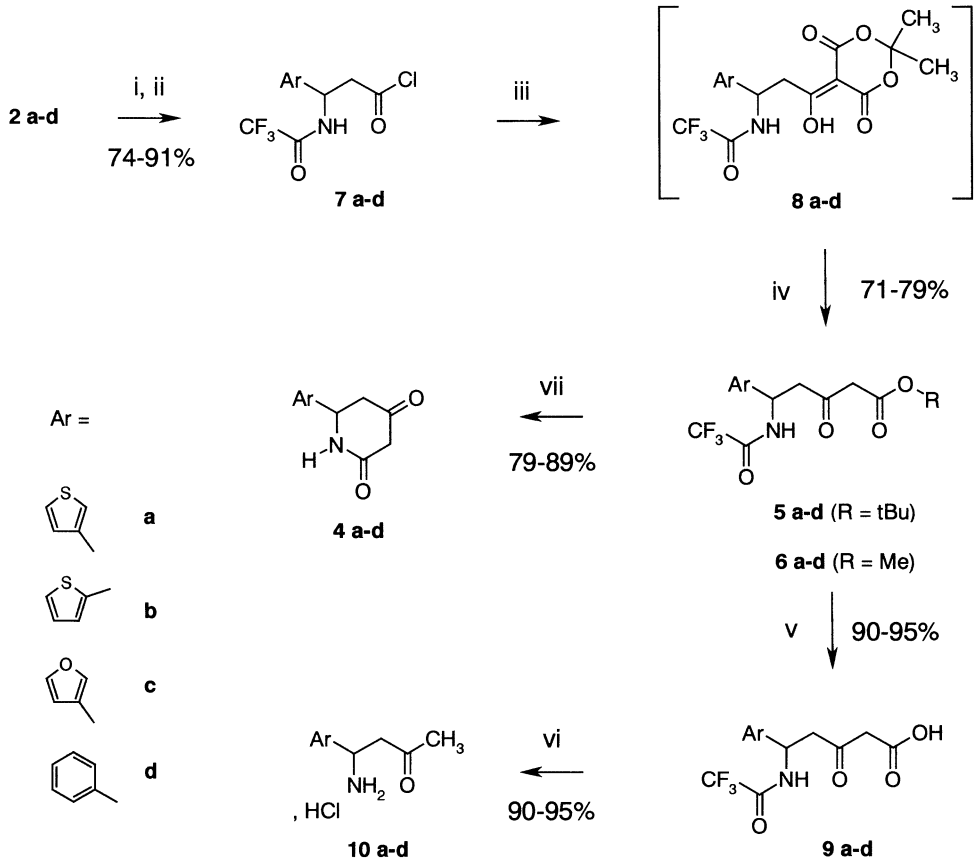
Yields of this sequence, ranging from 71 to 79%, were higher than those obtained with treatment of **7a–d** by ethyl malonate magnesium or lithium salts.[10,11]

The potential interest of δ-aryl-δ-trifluoroacetylamino-β-ketoesters **5a–d** and **6a–d**, as useful building blocks, prompted us to study the conditions of their *O* and *N* deprotection. Whilst, methyl esters **6a–d** did not lend themselves to hydrolysis, *tert*butyl derivatives **5a–d**, led in trifluoroacetic acid at room temperature to the δ-aryl-δ-trifluoroacetylamino-β-ketoacids **9a–d**, in near-quantitative yields. Removal of the trifluoroacetic group of **9a–d** occurred in refluxing aqueous hydrochloric acid solution, but with subsequent decarboxylation, yielding the aminoaryl-butanone hydrochloric salts **10a–d**.

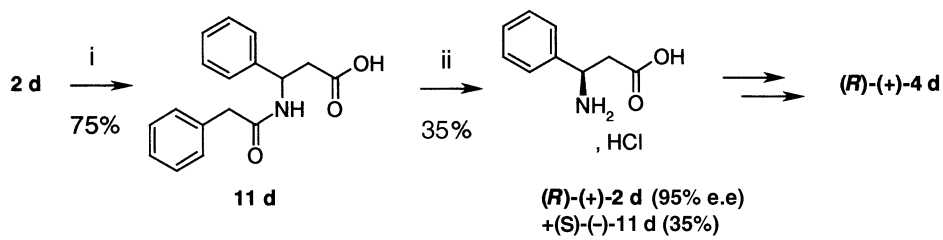
Finally, cyclisation of **5a–d** or **6a–d** was achieved by a mild alkaline treatment, using a 2N aqueous NaOH solution in THF, to give in 79–89% yields **4a–d**[12] among which **4d** was the sole hitertho reported 6-arylpiperidine-2,4-dione.[8]

The same general pathway, applied for example to (*R*)-(+) 3-amino-3-phenylpropionic acid **2d**, issued from the penicillin acylase-catalysed hydrolysis of the corresponding *N*-phenylacetyl derivative **11d**, according to the Soloshonok procedure,[13] led without racemisation to (*R*)-(+) **4d** (Scheme 3).[14]

In summary, this paper describes a very easy, cheap and versatile preparation of the title compounds. The biological evaluation of **4a–d** and related compounds



Scheme 2. (i) TFA/TFA_2O; (ii) $(ClCO)_2/CH_2Cl_2$; (iii) Meldrum's acid/pyridine/CH_2Cl_2; (iv) MeOH or *tert*BuOH; (v) TFA/CH_2Cl_2; (vi) (6N) HCl/H_2O; (vii) (2N) $NaOH/H_2O$/THF.



Scheme 3. (i) $ClCOCH_2C_6H_5/H_2O/Me_2CO$; (ii) penicillin acylase/$NaHCO_3/H_2O$.

and the chemical reactivity of **5**, **6** are currently under investigation.

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12. The experiment is as follows: Synthesis of **4a**. To a solution of **2a** (0.03 mol) in trifluoroacetic acid (10 ml), was added trifluoroacetic anhydride (0.075 mol) and the reaction mixture was stirred for 1 h at rt. The solvent was evaporated under reduced pressure and the oily residue was poured into a saturated aqueous $NaHCO_3$ solution. The aqueous layer was washed with diethyl ether (50 ml), acidified to pH 1 with an aqueous HCl (6N) solution and extracted twice with diethyl ether (50 ml). The combined organic layers were dried over magnesium sulfate and evaporated to dryness. To a solution of the residue in dry methylene chloride (50 ml), was added oxalyl chloride (0.15 mol) and the reaction mixture was refluxed for 3 h. The solvent was evaporated under reduced pressure to afford **7a** (88%). A mixture of Meldrum's acid (0.021 mol) and pyridine (0.05 mol) in dry methylene chloride (50 ml) was stirred for 0.5 h at rt. The reaction mixture was then cooled at 0°C and **7a** (0.02 mol) was added dropwise. The reaction mixture was quenched after 2 h at 0°C by adding an aqueous HCl (1N) solution and extracted twice with methylene chloride (50 ml). The combined organic layers were dried over calcium chloride and evaporated in vacuo. The Meldrum's adduct **8a** was refluxed for 4 h in methanol (50 ml) and evaporated to dryness. The oily residue was dissolved in methylene chloride (50 ml), washed with a saturated aqueous $NaHCO_3$ solution, dried over calcium chloride and evaporated to dryness to give **6a** (79%). To a stirred solution of **6a** (0.02 mol) in THF (20 ml) was added an aqueous NaOH (2N) solution (20 ml). After 2 h, the solution was acidified to pH 6.5 with an aqueous HCl (1N) solution and extracted twice with methylene chloride (25 ml). The combined organic layers were dried over calcium chloride and evaporated in vacuo to give **4a** (84%) as white crystals. Mp: 174°C; IR (KBr) 3183, 1716, 1668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.93 (2H, ddd, $J=4.5$, 8.3 and 16.3 Hz, CH_2), 3.34 (2H, dd, $J=19.9$ and 19.9 Hz, CH_2), 4.95 (1H, m, CH), 6.42 (1H, bs, NH), 7.04 (1H, dd, $J=1.0$ and 4.9 Hz, $H_{arom.}$), 7.23 (1H, dd, $J=1.0$ and 2.9 Hz, $H_{arom.}$), 7.40 (1H, dd, $J=2.9$ and 4.9 Hz, $H_{arom.}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 46.0, 47.4, 48.7, 122.1, 125.1, 128.1, 140.2, 168.7, 202.1. Anal. calcd for $C_9H_9NO_2S$: C, 55.37; H, 4.65; N, 7.17. Found: C, 55.62; H, 4.59; N, 6.88.
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14. (*R*)-(+) **4d**: $[\alpha]_D^{20}=124.9$ (*c* 0.025 MeOH), [lit.[8]: $[\alpha]_D^{20}=124.3$ (*c* 0.37, $CHCl_3$).