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Tetrahedron Letters 41 (2000) 681–683

TETRAHEDRON  
LETTERS

## Efficient synthesis of 2-aryl-6-methyl-2,3-dihydro-1*H*-pyridin-4-ones

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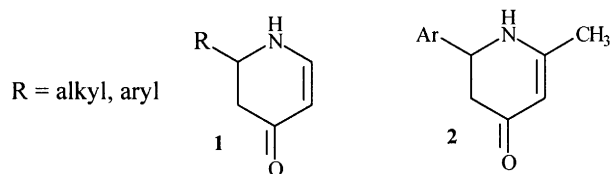
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Received 18 October 1999; accepted 17 November 1999

### Abstract

Syntheses of 2-aryl-6-methyl-2,3-dihydro-1*H*-pyridin-4-ones were achieved starting from corresponding  $\beta$ -aryl- $\beta$ -amino acids. This reaction sequence involved, as a key step, the condensation of an acid chloride with a diketone using  $\text{SmI}_3$  as catalyst. A final intramolecular cyclization furnished the attempted product. © 2000 Elsevier Science Ltd. All rights reserved.

Dihydropyridones of the type **1** (Scheme 1) are interesting building blocks for a large variety of heterocycle syntheses,<sup>1</sup> because their amino-enone moiety can be used in various reactions, such as 1,2- and 1,4-additions, electrophilic substitutions and enolate alkylations. This type of compound can be prepared according to two general routes, cyclization of triketones with ammonia,<sup>2,3</sup> or addition of organometallics to 1-acyl salts of 4-methoxypyridines.<sup>4–6</sup> Moreover, they are also of great interest in medicinal chemistry to design ligands for the neuronal nicotinic receptor.<sup>7</sup>

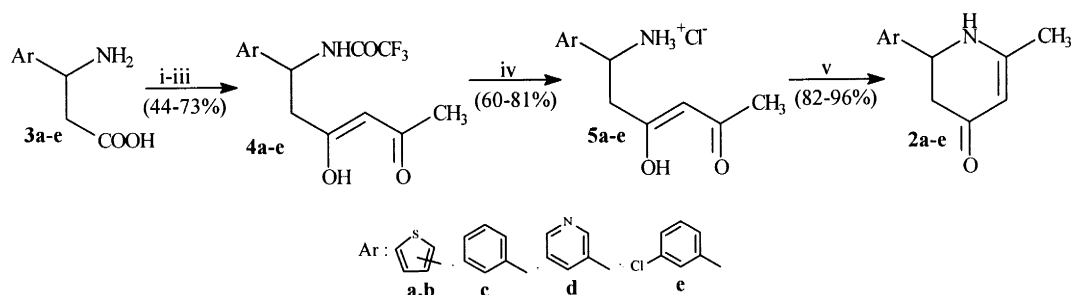


Scheme 1.

We wish to present herein a new efficient pathway which starts from  $\beta$ -amino- $\beta$ -arylpropionic acids and, in five steps, authorizes the preparation of a large diversity of compounds of the type **2**. Thus, the sequence depicted in Scheme 2 is as follows: the  $\beta$ -amino acids **3** were prepared according to the Rodionow–Johnson's method<sup>8,9</sup> from the corresponding arylaldehydes. The amino function was then protected by the trifluoroacetyl group, and then the acid chlorides were prepared in refluxing

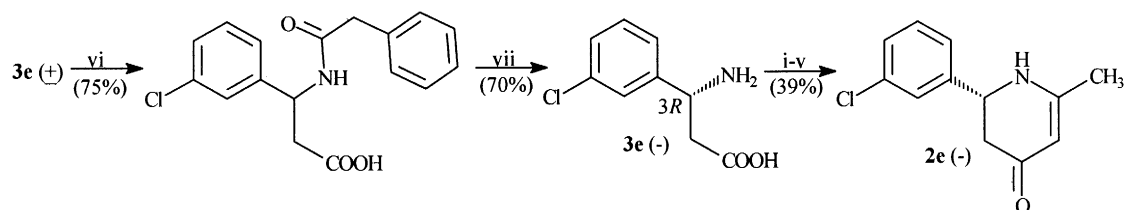
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thionyl chloride. The latter were converted into the trifluoroacetyl-amino- $\beta$ -diketones **4** by reaction with acetylacetone in the presence of samarium iodide according to the method recently described by Hao.<sup>10</sup> Deprotection of the amino group in boiling hydrochloric acid gave the stable ammonium salts **5** which underwent an intramolecular cyclization in alkaline medium to give the 2-aryl-6-methyl-1,2-dihydropyridin-4-ones **2** in high yield (Scheme 2). Furthermore, we have demonstrated that this sequence can be applied to obtain enantiopure pyridones **2** using chiral  $\beta$ -amino acids.<sup>11</sup>



Scheme 2. (i) (CF<sub>3</sub>CO)<sub>2</sub>O; (ii) SOCl<sub>2</sub>; (iii) SmI<sub>2</sub>/CH<sub>3</sub>COCH<sub>2</sub>COCH<sub>3</sub>/CH<sub>3</sub>CN; (iv) HCl (6N)/ $\Delta$ ; (v) NH<sub>4</sub>OH

Thus, application of this sequence to (-)-(2*R*)-2-(3-chlorophenyl)-3-aminopropionic acid **3e**<sup>11</sup> (Scheme 3) gave (-)-(2*R*)-2-(3-chlorophenyl)-6-methyl-1,2-dihydropyridin-4-one **2e**<sup>12</sup> without racemization (ee >95%, determined by chiral HPLC analysis).



Scheme 3. (vi) C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>COCl/Et<sub>3</sub>N/CH<sub>3</sub>COCH<sub>3</sub>/H<sub>2</sub>O; (vii) penicillin acylase (*E. coli*)/NaHCO<sub>3</sub>/H<sub>2</sub>O

## References

- Chen, C.; McDonald, I. A.; Munoz, B. *Tetrahedron Lett.* **1998**, *39*, 217–220.
- Work, S. D.; Hauser, C. R. *J. Org. Chem.* **1963**, *28*, 725–730.
- Stout, D. M.; Meyers, A. I. *Chem. Rev.* **1982**, *82*, 223–243.
- Comins, D. L.; Brown, J. D. *Tetrahedron Lett.* **1986**, *27*, 4549–4552.
- Comins, D. L.; Killpack, M. O. *J. Am. Chem. Soc.* **1992**, *114*, 10972–10974.
- Comins, D. L.; Joseph, S. P.; Goehring, R. R. *J. Am. Chem. Soc.* **1994**, *116*, 4719–4728.
- Holladay, M. W.; Dart, M. J.; Lynch, J. K. *J. Med. Chem.* **1997**, *40*, 4170–4194.
- Rodionow, W. M.; Malewinskaja, E. T. *Chem. Ber.* **1926**, *59*, 2952–2958.
- Johnson, T.; Livak, J. E. *J. Am. Chem. Soc.* **1936**, *58*, 299–303.
- Hao, W.; Zhang, Y.; Ying, T.; Lu, P. *Synth. Commun.* **1996**, *26*, 2421–2427.
- Soloshonok, V. A.; Fokina, N. A.; Rybakova, A. V.; Shishkina, I. P.; Galushko, S. V.; Sorochinsky, A. E.; Kukhar, V. P.; Savchenko, M. V.; Svedas, V. K. *Tetrahedron: Asymmetry* **1995**, *6*, 1601–1610.
- The experiment is as follows: Synthesis of **2e**. A mixture of powdered samarium (0.037 mol) and iodine (0.061 mol) in dry acetonitrile (300 mL) was stirred at room temperature until the samarium disappeared. To the cooled resulting suspension of SmI<sub>2</sub> were added the acid chloride (0.034 mol) and pentane-2,4-dione (0.037 mol). The reaction mixture was stirred for 6 h at 0°C. It was then treated with dilute hydrochloric acid and extracted with diethyl ether (3×100 mL). The combined organic layers were washed with saturated aqueous NaHCO<sub>3</sub> and Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solutions, dried over magnesium sulfate and evaporated

to dryness. The residue was refluxed for 12 h in aqueous HCl solution (6N), then filtered and evaporated to dryness to give the ammonium salt **5e**. A suspension of **5e** (0.0072 mol) in 100 mL of methylene chloride was made alkaline to pH=10 with an ammonium hydroxide solution. It was then extracted with methylene chloride (2×50 mL). The combined organic layers were dried over calcium chloride and evaporated to dryness. The oily residue was triturated in diethyl ether to give **2e** as beige crystals: mp: 129°C; IR (KBr) 3220, 1615  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.86 (3H, s,  $\text{CH}_3$ ), 2.26 (1H, dd,  $J=105.9$  and 5.6, H-3a), 2.36 (1H, dd,  $J=15.9$  and 11.2, H-3b), 4.65 (2H, m, H-2' and H-5'), 7.29 (3H, m,  $\text{H}_{\text{arom}}$ ), 7.39 (1H, s,  $\text{H}_{\text{arom}}$ ), 7.72 (1H, broad s, NH);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  20.2, 42.8, 55.7, 97.7, 125.5, 126.7, 127.6, 130.4, 133.2, 143.7, 162.5, 189.0;  $[\alpha]_{\text{D}}^{25} = -176.92$  (c, 0.004  $\text{CH}_3\text{OH}$ ); anal. calcd for  $\text{C}_{12}\text{H}_{12}\text{ClNO}$ : C, 65.02; H, 5.91; N, 6.32. Found: C, 64.89; H, 6.02; N, 6.25.