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SYNTHESIS OF 6-*tert*-BUTYL-2-ARYLPYRIDINES [+]

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Abstract: The title compounds were prepared from aryl β-ketoesters in a simple two step procedure.

In connection with another project we required access to a series of 6-*tert*-butyl-2-arylpyridines. A review of the literature revealed two references to the simplest compound of the series, 6-*tert*-butyl-2-phenylpyridine; the other compounds are unreported. 6-*tert*-Butyl-2-phenylpyridine has been characterised as a component of the mixture resulting from the free radical alkylation of pyridine with *tert*-butyl mercuric chloride[1]. It has also been synthesised from the oxime of 2,2 dimethyl-3-oxo-7-phenylhepta-4,6-diene under palladium catalysis[2]; however, the yield was poor (30%). We therefore devised a route (Scheme I) to these compounds which we believe to be general.

[+] This paper is dedicated to the memory of Rick Keeling, a fine teacher.

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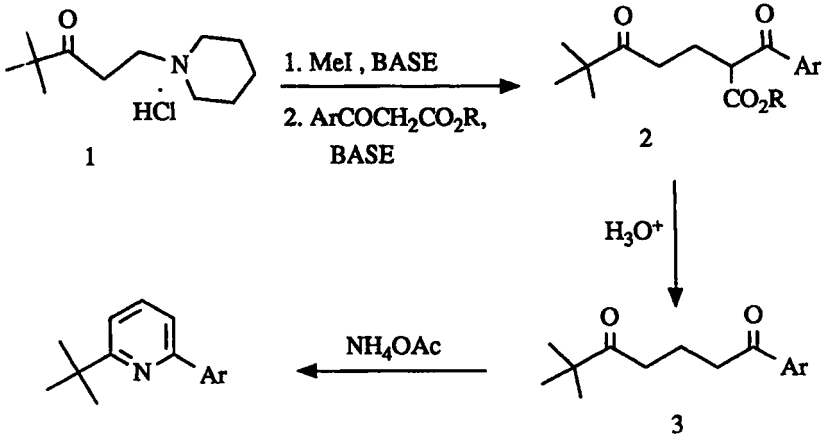
Scheme I



Ar = Ph, 2-F-Ph, 4-Me-Ph, 4-MeO-Ph, 4-NO_2-Ph, 2-Thienyl, 1-Naphthyl

The starting material 4,4-dimethyl-1-piperidinopentan-3-one hydrochloride (1) is available from piperidine hydrochloride, pinacolone and paraformaldehyde by standard Mannich chemistry[3]. This material was neutralised (K_2CO_3 / MeCN), quaternised (MeI / MeCN) and reacted with the requisite aryl β-ketoester (K_2CO_3 / MeCN) to give (2). The crude reaction product mixture was hydrolysed and decarboxylated with concentrated hydrochloric acid to give the 1,5-diketone (3) in fair yield based on starting aryl β-ketoester (Table I). Base hydrolysis of (2) gives the benzoic acid. Cyclisation of (3) under the literature conditions[4] (NH_4OAc/AcOH) gives the required 6-*tert*-butyl-2-arylpyridine in good yield (Table I). All products were characterised by ^1H N.M.R, I.R. and high resolution M.S.

EXPERIMENTAL: 4,4-Dimethyl-1-piperidinopentan-3-one hydrochloride (2.33g, 10mmol) was suspended in dry acetonitrile (30ml), potassium carbonate (1.38g,

Table I

Ar	Yield of 3*	Yield of Pyridine
Ph	47	76
2-F-Ph	47	82
4-MeO-Ph	52	74
4-Me-Ph	48	78
4-NO_2-Ph	49	79
2-Thienyl	46	71
1-Naphthyl	55	65

*yield % w.r.t. Aryl β-ketoester refers to material isolated after column chromatography.

10mmol) was added and the mixture was heated briefly to reflux. The mixture was cooled (ice / water bath) to 5^0C and iodomethane (1.4g, 10mmol) was added. The mixture was stirred for 30 mins and allowed to warm to room temperature. Ethyl benzoylacetate (1.92g, 10mmol) was added followed by potassium carbonate (1.38g, 10mmol). The mixture was heated under reflux for 15 hours under N_2 and filtered to remove inorganics. The filtrate was concentrated under reduced pressure, taken up in dichloromethane and washed with dilute hydrochloric acid. The organic phase was dried ($MgSO_4$), filtered and evaporated to give a brown oil (3.74g) which solidified on standing. The crude product was heated under reflux with concentrated hydrochloric acid (60ml) for 15 hours, cooled and extracted into dichloromethane. The organic phase was collected, dried ($MgSO_4$), filtered and evaporated to give the crude product as a dark oil (2.3g). This was purified by flash column

chromatography on silica (eluent, hexane / ethyl acetate 4:1) to give 6,6-dimethyl-1-phenylheptan-1,5-dione as a yellow oil (1.1g, 4.7mmol).

This material was dissolved in glacial acetic acid (20ml) and ammonium acetate (2.8g,36mmol) was added. The mixture was heated under reflux for 2 hours and then the solvent was removed under reduced pressure. The crude product was taken up in dichloromethane and washed with 2N sodium hydroxide solution, the organic phase was dried ($MgSO_4$), filtered and evaporated. The product was purified by flash column chromatography on silica (eluent, hexane / ether 19:1) to give 6-*tert*-butyl-2-phenylpyridine as a colourless oil (765mg, 36mmol).

6,6-Dimethyl-1-phenylheptan-1,5-dione

M^+ found 232.1466 $C_{15}H_{20}O_2$ requires 232.1463

^1H N.M.R. 1.14 9H(s), 2.01 2H(m), 2.63 2H(t), 3.00 2H(t), 7.46 2H(m), 7.56 1H(m), 7.97 2H(m).

I.R. 2967, 1703, 1701,1407 cm^{-1}.

6-*tert*-Butyl-2-phenylpyridine

M^+ found 211.1360 $C_{15}H_{17}N$ requires 211.1361

^1H N.M.R. 1.42 9H(s), 7.26 1H(m), 7.35-7.49 3H(m), 7.54 1H(m), 7.65 1H(m), 8.10 2H(m).

I.R. 2961, 1571, 1457 cm^{-1}.

6,6-Dimethyl-1-(2-fluorophenyl)heptan-1,5-dione

M^+ found 250.1374 $C_{15}H_{19}FO_2$ requires 250.1369

^1H N.M.R. 1.14 9H(s), 1.99 2H(m), 2.61 2H(m), 3.01 2H(m), 7.13 1H(m), 7.23 1H(m), 7.51 1H(m), 7.86 1H(m).

IR. 2969, 1705,1688,1610, 1480, 1452 cm^{-1}.

6-*tert*-Butyl-2-(2-fluorophenyl)pyridine

M^+ found 229.1267 $C_{15}H_{16}FN$ requires 229.1267

^1H N.M.R. 1.42 9H(s), 7.14 1H(ddd),7.26 1H(dt), 7.28 1H(m), 7.32 1H(m), 7.63-7.69 2H(m), 8.14 1H(dt).

I.R. 2957, 1589, 1576, 1490,1457 cm^{-1}.

6,6-Dimethyl-1-(4-nitrophenyl)heptan-1,5-dione

M^+ found 277.1315 $C_{15}H_{19}NO_4$ requires 277.13.14

^1H N.M.R. 1.15 9H(s), 2.02 2H(m), 2.66 2H(m), 3.05 2H(m), 8.13 2H(d), 8.32 2H(d).

I.R. 2974,1700,1695,1520 1346 cm^{-1}.

6-*tert*-Butyl-2-(4-nitrophenyl)pyridine

M^+ found 256.1214 $C_{15}H_{16}N_2O_2$ requires 256.1212

^1H N.M.R. 1.44 9H(s), 7.38 1H(dd), 7.64 1H(dd), 7.74 1H(dd), 8.26 2H(d), 8.32 2H(d).

I.R. 2954, 1585,1510,1339 cm^{-1}.

6,6-Dimethyl-1-(4-methoxyphenyl)heptan-1,5-dione

M^+ found 262.1554 $C_{16}H_{22}O_3$ requires 262.1569

^1H N.M.R. 1.13 9H(s), 1.99 2H(m), 2.62 2H(t), 2.94 2H(t),3.87 3H(s), 6.93 2H(d), 7.96 2H(d).

I.R. 2969, 1705, 1675, 1601, 1260 cm^{-1}.

6-*tert*-Butyl-2-(4-methoxyphenyl)pyridine

M^+ found 241.1455 $C_{16}H_{19}NO$ requires 241.1466

^1H N.M.R. 1.41 9H(s), 3.86 3H(s), 6.98 2H(d), 7.20 1H(dd), 7.47 1H(dd), 7.62 1H(t), 8.05 2H(d).

I.R. 2958, 1609, 1588,1514,1449, 1253 cm^{-1}.

6,6-Dimethyl-1-(4-methylphenyl)heptan-1,5-dione

M^+ found 246.1619 $C_{16}H_{22}O_2$ requires 246.1620

^1H N.M.R. 1.13 9H(s), 1.99 2H(m), 2.40 3H(s), 2.62 2H(t), 2.97 2H(t), 7.25 2H(d), 7.86 2H(d).

I.R. 2968, 1705, 1701, 1608, 1366 cm^{-1}.

6-*tert*-Butyl-2-(4-methylphenyl)pyridine

M^+ found 225.1516 $C_{16}H_{19}N$ requires 225.1518

^1H N.M.R. 1.42 9H(s), 2.39 3H(s), 7.20-7.27 3H(m), 7.62 1H(m), 7.50 1H(m), 7.99 2H(d).

I.R. 2955, 1577, 1447 cm^{-1}.

6,6-Dimethyl-1-(2-thienyl)heptan-1,5-dione

M^+ found 239.1110 $C_{13}H_{18}O_2S$ requires 239.1106

^1H N.M.R. 1.13 9H(s), 2.01 2H(m), 2.63 2H(t), 2.94 2H(t), 7.13 1H(dd), 7.63 1H(d), 7.75 1H(d).

I.R. 2967, 1703, 1701, 1417 cm^{-1}.

6-*tert*-Butyl-2-(2-thienyl)pyridine

M^+ found 218.1003 $C_{13}H_{15}NS$ requires 218.1003

^1H N.M.R. 1.40 9H(s), 7.08 1H(dd), 7.17 1H(dd), 7.34 1H(d), 7.43 1H(dd), 7.57 1H(d), 7.59 1H(t).

I.R. 2963, 1583, 1573, 1453 cm^{-1}.

6,6-Dimethyl-1-(1-naphthyl)heptan-1,5-dione

M^+ found 283.1698 $C_{19}H_{22}O_2$ requires 283.1698

^1H N.M.R. 1.14 9H(s), 2.06 2H(m), 2.66 2H(t), 3.08 2H(t), 7.4-7.6 3H(m), 7.8-7.9 2H(m), 7.98 1H(m), 8.58 1H(d).

I.R. 2968, 1703, 1700, 1507 cm^{-1}.

6-*tert*-Butyl-2-(1-naphthyl)pyridine

M^+ found 262.1588 $C_{19}H_{19}N$ requires 262.1596

^1H N.M.R. 1.44 9H(s), 7.36 1H(m), 7.38 1H(m), 7.48 2H(m), 7.56 1H(m), 7.64 1H(m), 7.74 1H(m), 7.90 2H(m), 8.29 1H(m).

I.R. 2954, 1571, 1445 cm^{-1}.

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