Total synthesis of $\text{n-methyl-n-formyltyramine}$, a new $\beta$-phenethylamide derivative isolated from $\text{cyathobasis fruticulosa}$ (bunge) aellen

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Introduction

The family of $\beta$-phenethylamides, exemplified by compounds 1 and 2 (Bohlmann et al., 1984) comprises a large number of substances widely distributed in nature. These substances have been found mostly in the cell wall soluble fractions of higher plants (Martin-Tanguy et al., 1978).

Many $\beta$-phenethylamides have been found in different plant species (Suzuki et al., 1981; Adesina et al., 1988; Adesina and Reisch, 1989; Horio et al., 1993; Cutillo et al., 2003; Kim et al., 2005), and $N$-trans-feruloyltyramine (3) has already been isolated from several plant sources (Yoshihara et al., 1978; Hussain et al., 1982; Fukuda et al., 1983; Achenbach et al., 1991; Gözler et al., 1992; Rahman et al., 1992; Lajide et al., 1995; Claros et al., 2000; Seca et al., 2001). Although there is yet no definitive conclusion about the function of these compounds in plants, a main role in growth and also self-defense processes has been proposed, especially because of its antimicrobial and antiviral effects (Martin-Tanguy, 1985; Martin-Tanguy and Negrel, 1987). Besides, $\beta$-phenethylamides such as 4-7 have been reported to have diverse and interesting biological activity from DNA strand scission (Ma et al., 2004) to antimutagenic and anticarcinogenic properties (Milić and Milić, 1998). Research groups have noted that these compounds inhibit lipopolysaccharide-induced nitric oxide production in macrophages (Tanaka et al., 1989; Kim et al., 2003), and also inhibit acetylcholinesterase (Kim and Lee, 2003). It is worth to mention that $N$-acetyltyramine (8) is an inducible phytoalexine, found in soy seeds (Garcez et al., 2000). On the other hand, Paik et al. (2001) have reported the isolation of the unusual compounds 9-11 in Xenorhabdus nematophilus, a bacterial strain that grows symbiotically with a nematode. These $\beta$-phenethylamides have shown cytotoxic activity against five cell lines of human cancer (Paik et al., 2001).
Recently, Topçu et al. (Bahceevli et al., 2005) isolated \(N\)-methyl-\(N\)-formlytyramine (12) from the aerial parts and roots of Cyathobasis fruticulosa (Bunge) Aellen (Chenopodiaceae), the only species of the genus Cyathobasis found in the flora of Turkey, specifically in the region of Central Anatolia.

Taking into account the potential interest in this class of compounds, it was decided to carry out the total synthesis of the \(\beta\)-phenethylamides 12 from commercial 4-hydroxybenzaldehyde (13).

**Methodology**

For carrying out this synthesis usual work procedures of the laboratory of organic synthesis were followed. Reactions were carried out in glass material dried in oven and under nitrogen or argon atmosphere. All compounds led to unique spots when subjected to different TLC conditions.

Spots were visualized under UV light (254 and 365 nm), followed by spraying with appropriate reagents (ethanolic ninhydrin, \(p\)-anisaldehyde/\(H_2SO_4\)/EtOH, Dragendorff). The final purification of each intermediate was carried out by column chromatography on silica gel 60H, eluting with mixtures of hexane/ethyl acetate under positive pressure using the gradient technique unless stated otherwise.

IR spectra were performed on a Shimadzu IR Prestige 21 spectrophotometer. \(^1\)H and \(^13\)C Nuclear Magnetic Resonance spectra were recorded in an AC200-E Bruker spectrometer (at 200.13 and 50.33 MHz, respectively). HRMS were made by Kent Electronics (UK).

Physical data of \(N\)-[2\('\)-(4-hydroxyphenyl)ethyl]-\(N\)-methylformamide 12 (\(N\)-methyl-\(N\)-formlytyramine):

**IR (KBr) \(\text{vmax/cm}^{-1}\):** 3141, 3135, 2945, 2924, 2882, 1657, 1652, 1614, 1595, 1509, 1446, 1394, 1239, 1172, 1072, 816, 768, 655 \(\text{cm}^{-1}\); \(^1\)H-NMR (\(\delta\)) Z-form: 2.71-2.80 (m, 2H, \(\text{ArCH}_2\text{CH}_2\text{N}\)), 2.86 (s, 3H, \(\text{NCH}_3\)), 3.55 (t, \(J=7.1\), 2H, \(\text{ArCH}_2\text{CH}_2\text{N}\)), 6.75 (d, \(J=8.2\), 2H, H-3 and H-5), 6.92 (t, \(J=8.2\), 2H, H-2 and H-6), 7.97 (s, 2H, ArOH and NCHO); \(E\)-form: 2.71-2.80 (m, 2H, \(\text{ArCH}_2\text{CH}_2\text{N}\)), 2.90 (s, 3H, \(\text{NCH}_3\)), 3.42 (t, \(J=6.5\), 2H, \(\text{ArCH}_2\text{CH}_2\text{N}\)), 6.72 (d, \(J=8.0\), 2H, H-3 and H-5), 7.03 (t, \(J=8.0\), 2H, H-2 and H-6), 7.66 (s, 1H, NCHO), 7.97 (s, 2H, ArOH and NCHO);

\(^13\)C-NMR (\(\delta\)) Z-form: 32.0 (C-2'), 34.9 (NCH), 45.9 (C-1'), 115.4 (C-3 and C-5), 129.0 (C-1'), 129.5 (C-2 and C-6), 155.2 (C-4), 162.8 (NCHO); \(E\)-form: 29.9 (C-2'), 33.4 (NCH), 51.7 (C-1'), 115.7 (C-3 and 5), 128.2 (C-1'), 129.6 (C-2 and C-6), 155.3 (C-4), 163.2 (NCHO);

**HRMS (IQ):** 180.10254 (\(M^+ + 1\)); \(C_{10}H_{14}NO_2\) requires 180.10245.

**Results**

The synthesis of the amide 12 began with Williamson’s etherification of the hydroxyaldehyde 13 and benzyl chloride, giving rise to the ether 14 in almost quantitative yields (Scheme). This ether was subjected to Henry’s condensation with nitromethane in the presence of ethylenediammonium diacetate as base (Barton et al., 1982) leading the nitrostyrene 15 in 90% yield. This, in turn, was reduced with LiAlH\(_4\) to the corresponding phenethylamine (16), which proved to be unstable, thus darkening easily on contact with air. Therefore, to prevent degradation 16 was converted directly, without previous purification, to the formamide 17 by treatment with ethyl formate under reflux. The crude product by chromatography led to the amide 17 in 44% yield for both combined steps (reduction-formamidation). It is interesting to emphasize that in \(^1\)H- and \(^13\)C-NMR spectra 17 exhibited signals consistent with the presence of two conformers, these being distinguished yet at 70°C in DMSO-\(d_6\).

Continuing the sequence, the amide 17 was \(N\)-methylated with methyl iodide in DMF using NaH as base, thus obtaining after purification by column chromatography, 79% of the intermediate 18. The removal of the benzyl ether of 18 by catalytic hydrogenation in the presence of 10% Pd/C in absolute EtOH, allowed to have the final product 12 in 92% yield.
It was observed that $^1$H- and $^{13}$C-NMR spectra of the synthetic product 12 were in complete agreement with those reported in the literature for the natural compound. In both spectra of 12 and 18 the presence of two conformers was found as indicated for formamide 17.

Conclusions

The total synthesis of 12 has been carried out in 6 steps from commercial $p$-hydroxybenzaldehyde in a 25% overall yield.

The initial protection of the phenol as benzyl ether allowed adequate handling of reaction intermediates, without loss of efficiency in the synthetic sequence.

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