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Synthesis of the seed germination stimulant 3-methyl-2*H*-furo[2,3-*c*]pyran-2-one

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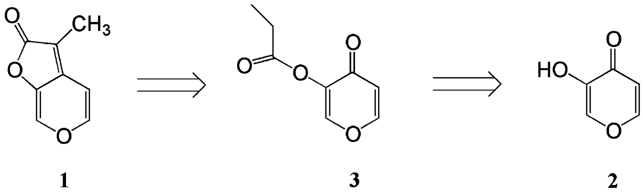
Abstract—3-Methyl-2*H*-furo[2,3-*c*]pyran-2-one **1** was recently identified as the key agent in smoke, responsible for promoting the seed germination of a diverse range of fire-dependent and fire-independent plant species from around the world. The synthesis of this novel compound, obtained in three steps from pyromeconic acid, is described.

1. Introduction

Recently, we have reported the isolation of a compound from plant-derived smoke that is responsible for promoting the seed germination of a wide range of plant species from Australia, North America and South Africa.[1] The compound was identified as 3-methyl-2*H*-furo[2,3-*c*]pyran-2-one **1** on the basis of spectroscopic analysis (MS, ^{1}H NMR, ^{13}C NMR and 2D NMR). We now report the synthesis of this new bioactive compound.

2. Results and discussion

Retrosynthetic analysis of **1** (Scheme 1) indicated that pyromeconic acid **2** would provide a useful starting compound.[2] We envisaged that treatment of the propionyl ester of pyromeconic acid **3** with a strong base, such as lithium diisopropylamide (LDA), could lead to cyclisation and formation of the butenolide entity. This proved unsuccessful, so alternative methods for forming the butenolide were investigated.



Scheme 1. Retrosynthetic approach to 3-methyl-2*H*-furo[2,3-*c*]pyran-2-one **1**.

Other methods attempted included treatment of the propionyl ester **3** with acetic anhydride as described by Belsky et al.[3] Additionally, the analogous 2-chloropropionyl ester of pyromeconic acid was treated with triethylphosphite in an attempt to form the phosphonate, which could be treated under Horner–Emmons conditions to form the butenolide.[4,5] However, these methods failed to yield the desired product.

A more promising approach was the method described by Ohkata et al.[6] for forming vinylogous 4*H*-pyrones from 4*H*-pyran-4-thione and arenyl bromomethyl ketones. Thus, the 2-chloropropionyl ester of pyromeconic acid **4** was converted to the corresponding thione **5** by

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Keywords: Butenolide; Germination stimulant; Seed germination; Smoke.

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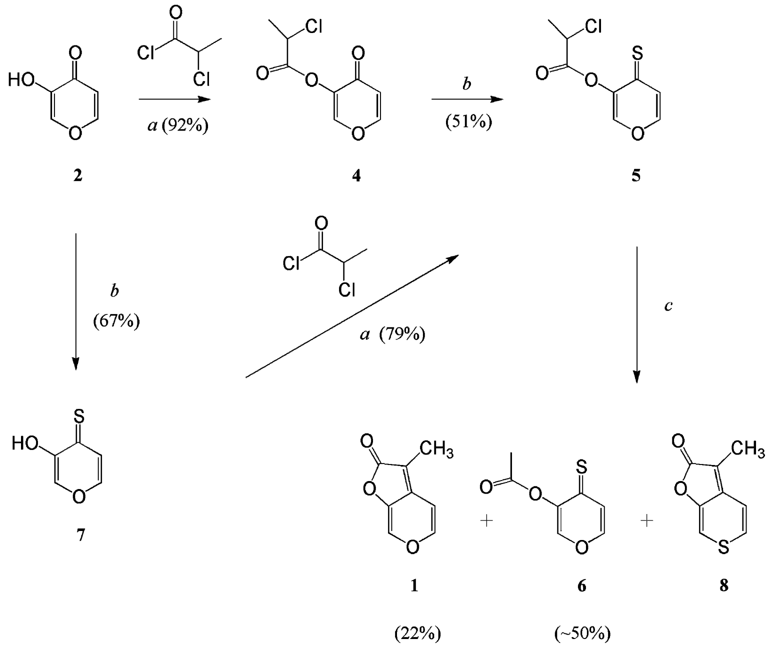

Scheme 2. Synthesis of 3-methyl-2*H*-furo[2,3-*c*]pyran-2-one **1**. Reagents and conditions: (a) 1.2 equiv Et_3N, CH_2Cl_2, 10 min, rt; (b) 1.5 equiv P_2S_5, 6 equiv $NaHCO_3$, THF, 3 h, rt; (c) 3 equiv NaOAc, 1.2 equiv Ph_3P, Ac_2O, 30 min, 140 °C. On heating concentrated solutions of **5** in acetic anhydride without Ph_3P, some of the thia analogue **8** was formed.

treatment with phosphorus pentasulfide.[7] Heating solutions of **5** in a range of solvents (e.g., acetone, acetonitrile, dioxane, anisole and dimethylformamide) under reflux failed to yield the expected 4-mercaptopyrylium salt. Heating **5** in acetic anhydride gave mainly the transesterification product **6**, together with a small amount of the target compound **1** (Scheme 2). Optimisation of the reaction conditions improved the yield of **1**, but the yield of the acetyl ester **6** was still high at approximately 50%. Isolation of the target compound though was readily achieved by hydrolysis of the reaction mixture, followed by extraction of **1** with dichloromethane. The synthetic sample of **1** was identical (UV, MS, ^{1}H NMR and ^{13}C NMR) to that isolated from smoke.[1]

A problem encountered in the formation of the thione ester **5** by treatment of the corresponding pyrone **4** with phosphorus pentasulfide was that almost 50% of the ester was hydrolysed to the pyromeconic acid thione **7**, thus requiring re-esterification. Treatment of pyromeconic acid **2** directly with phosphorus pentasulfide to form the corresponding thione **7**, followed by esterification with 2-chloropropionyl chloride to form **5**, was found to be more efficient (Scheme 2). It was also observed that heating concentrated solutions of **5** in acetic anhydride led to the formation of the sulfur analogue, 3-methyl-2*H*-thiopyran[3,4-*b*]furan-2-one **8** (Scheme 2), which was difficult to separate from **1** by chromatography. The addition of a thiophile,[8] such as triphenylphosphine, to the reaction mixture prevented this compound from forming and improved the yield of **1**.

In conclusion, we have achieved the first synthesis of 3-methyl-2*H*-furo[2,3-*c*]pyran-2-one **1** and confirmed the identity of the potent germination stimulant found in smoke.

3. Experimental

3.1. General procedure for the formation of 1

A mixture of anhydrous sodium acetate (280 mg, 3.4 mmol) and triphenylphosphine (330 mg, 1.3 mmol) in acetic anhydride was heated at 140 °C for 5 min. A solution of **5** (250 mg, 1.1 mmol) diluted with acetic anhydride (2 mL) was added dropwise to the heated mixture over 5 min. The mixture was heated for a further 30 min and allowed to cool. The dark reaction mixture was poured into ice/water (100 mL) and stirred until one phase was formed. The aqueous solution was filtered and extracted with dichloromethane (3 × 20 mL). The organic extract was washed with 1 M $NaHCO_3$ (2 × 20 mL), dried (Na_2SO_4), filtered and evaporated under reduced pressure. The residue was extracted with 0.2 M potassium carbonate solution (2 × 50 mL) by heating gently and the resulting yellow solution was filtered and extracted with dichloromethane (3 × 15 mL). The organic extract was washed with brine, dried (Na_2SO_4), filtered and evaporated under reduced pressure to give a yellow residue. The residue was purified by silica gel chromatography (30% ethyl acetate/light petroleum) to afford **1** as a light yellow crystalline solid (38 mg, 22%), which re-crystallised from light petroleum as light yellow needles (mp 118–119 °C).

Compound **1**: ^{1}H NMR (500 MHz, acetone-d_6): δ 7.77 (1H, s, H-7), 7.62 (1H, d, $J = 5.5$ Hz, H-5), 6.79 (1H, d, $J = 5.5$ Hz, H-4), 1.86 (3H, s, CH_3). ^{13}C NMR

(125.8 MHz, acetone-d_6): δ 171.1 (C=O), 149.8 (C-5), 143.0 (C-7a), 140.6 (C-3a), 128.0 (C-7), 104.1 (C-4), 100.0 (C-3), 7.6 (CH_3). HRMS calculated for $C_8H_6O_3$: 150.0317. Found: 150.0320. UV (λ_{max} in nanometers, $\log\varepsilon$): 347 (3.99), 330 (4.27), 320 (4.27), 242 (3.49), 202 (4.00). IR (CH_2Cl_2): 1746 cm^{-1} (C=O).

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Supplementary data

Supplementary data associated with this article can be found, in the online version at doi:10.1016/j.tetlet.2005.06.077.

References and notes

1. Flematti, G. R.; Ghisalberti, E. L.; Dixon, K. W.; Trengove, R. D. *Science* **2004**, *305*, 977.
2. Pyromeconic acid (**3**) was prepared from kojic acid as previously described: (a) Ellis, B. L.; Duhme, A. K.; Hider, R. C.; Hossain, M. B.; Rizvi, S.; Van der Helm, D. *J. Med. Chem.* **1996**, *39*, 3659–3670; (b) Öztürk, G.; Erol, D. D.; Uzbay, T.; Aytemir, M. D. *Il Farmaco* **2001**, *56*, 251–256.
3. Belsky, I.; Dodiuk, H.; Shvo, Y. *J. Org. Chem.* **1974**, *39*, 989–995.
4. Tanyeli, C.; Caliskan, Z. Z. *Synth. Commun.* **2000**, *30*, 2855–2862.
5. Demir, A. S.; Gercek, Z.; Duygu, N.; Igdir, A. C.; Reis, O. *Can. J. Chem.* **1999**, *77*, 1336–1339.
6. Ohkata, K.; Imagawa, M.; Akiba, K. *Heterocycles* **1986**, *24*, 2817–2820.
7. Scheeren, J. W.; Ooms, P. H. J.; Nivard, R. J. F. *Synthesis* **1973**, 149–151.
8. Roth, M.; Dubs, P.; Götschi, E.; Eschenmoser, A. *Helv. Chim. Acta* **1971**, *54*, 710–734.