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New efficient Synthesis of Furanoacetylene Phytoalexins Wyerone and Dihydrowyerone

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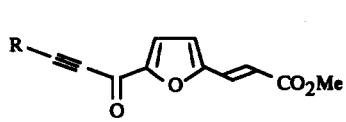
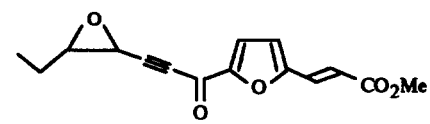
Key Words: Phytoalexins, dihydrowyerone, wyerone, N-methoxy-N-methylamides.

Abstract : *Furanoacetylene phytoalexins wyerone 1a and dihydrowyerone 1b were efficiently synthesized in multigram quantities starting from furfural. The key step involved an acylation by acetylenic N-methoxy-N-methylamides 3a,b.*

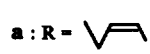
Phytoalexins are natural fungitoxic compounds which are produced by plants in response to fungal infections.[1] Numerous studies have established that the resistance to fungal diseases is strongly dependent to the importance and the rapidity of phytoalexins production. For instance, furanoacetylene phytoalexins, such as wyerone **1a**, dihydrowyerone **1b** and wyerone epoxide **2** have been isolated in small amounts from infected broad beans (*Vicia faba* L.; Fam. Papilionaceae).[2] Authentic standards of these phytoalexins were required in order to quantify their biological production. Furthermore substantial amounts of these products, and some selected analogs, were desirable in order to estimate their antifungal activity towards several fungi (*Botrytis, Ascochyta*). Previous syntheses of **1a** and **1b** rely on the condensation between methyl 3-(5-formyl-2-furyl)acrylate with appropriate Grignard reagents.[2,3] In a recent synthesis of dihydrowyerone, the ketone functionality was finally introduced by a palladium-catalyzed coupling of an acid chloride with an alkynylstannane.[4] In this paper, we report on an efficient synthesis of wyerone and dihydrowyerone making use of N-methoxy-N-methylamides **3** as highly effective acylating reagents.[5]

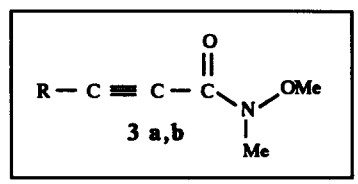


1a,b



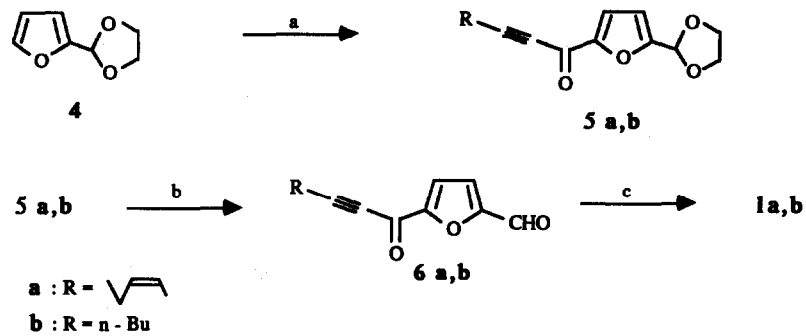
2

a : R = 
b : R = n - Bu



3 a,b

Condensation of 2-heptynoic acid with 1.1 equiv of N,O-dimethylhydroxylamine hydrochloride in the presence of 1.03 equiv of pyridine and 2 equiv of dicyclohexylcarbodiimide in acetonitrile afforded N-methoxy-N-methyl-2-heptynamide **3b** in 95% yield.[6] α-Lithiation of 2-(2-furanyl)-1,3-dioxolane **4**[7] using n-butyllithium followed by acylation using **3b**[8] afforded the acetylenic ketone **5b** in 79% yield.[9] Acidic cleavage of the dioxolane group (ether / 50% aq. H_2SO_4 2:1, rt, 15 h.) yielded quantitatively aldehyde **6b** which upon reaction with 1.23 equiv of trimethyl phosphonoacetate in the presence of 3 equiv of lithium hydroxide monohydrate in THF / water 5:1[10] furnished dihydrowyerone **1b** in 81% yield (64% overall yield from **3b** in 3 steps) which was separated by chromatography on silica gel from a small amount of less polar Z isomer (4%).



(a) n-BuLi, THF, -80°, 1h then **3a** or **3b**, -80°, 45 mn, 79%; (b) Et_2O / 50% aq. H_2SO_4 2:1, 20°, 15h, quant.; (c) $(MeO)_2P(O)CH_2CO_2Me$, LiOH, THF, 1h, 20°, 69% for **1a**, 81% for **1b**.

For the synthesis of wyerone **1a**, the introduction of the enyne unit was best performed by means of enynamide **3a**.[11] Propiolic acid was converted into N-methoxy-N-methyl-2-propynamide[12] in 60% yield as previously described for **3b**. Palladium-catalyzed coupling with (Z)-1-iodo-1-butene[13] using 0.05 equiv of tetrakis(triphenylphosphine)palladium(0) in the presence of 0.15 equiv of cuprous iodide and 2 equiv of triethylamine in toluene stereoselectively afforded (Z)-N-methoxy-N-methyl-4-hepten-2-ynamide **3a** in 50% yield.[14] Acylation of **4** by **3a** via its α-lithio derivative followed by dioxolane cleavage as previously described afforded aldehyde **6a**. Condensation with trimethyl phosphonoacetate then afforded wyerone, **1a**, in 69% yield (27% overall yield from known (Z)-1-iodo-1-butene in 4 steps) after chromatographic separation from a small amount (7%) of Z-isomer. These compounds were characterized by their spectroscopic and analytical properties.[15]

In summary, these short and efficient syntheses starting from a cheap furan precursor (furfural) enabled to obtain multigram quantities of wyerone and dihydrowyerone required for biological studies. Furthermore, the present strategy appears versatile and could be used to prepare new analogs by using other phosphonate reagents in the last step. The potential of acetylenic N-methoxy-N-methylamides is also illustrated in these syntheses.

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References and Notes

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5. Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815 - 3818.
6. N-Methoxy-N-methyl-2-heptynamide **3b**: ^{1}H NMR ($CDCl_3$, 90 MHz) δ 3.77 (s, 3H, OCH_3), 3.26 (broad s, 3H, NCH_3), 2.39 (t, 2H, J = 6.7 Hz, $C{\equiv}C\text{-}CH_2$), 1.80 - 1.20 (m, 4H, $CH_2CH_2CH_3$), 0.93 (t, 3H, J = 6.6 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ 154.21 (CO), 93.53 (C≡C-CO), 73.35 (C≡C-CO), 61.74 (OCH_3), 33.2 (NCH_3), 29.85 ($CH_2CH_2CH_3$), 21.94 (CH_2CH_3), 18.66 ($C{\equiv}C\text{-}CH_2$), 13.49 (CH_3).
7. 2-(2-Furanyl)-1,3-dioxolane was prepared by protection of furfural similarly to known procedures[16] (toluene as solvent, *p*-toluenesulfonic acid monohydrate as catalyst, 8 hours reflux, 85%).
8. To a solution of 2-(2-furanyl)-1,3-dioxolane (5.7 mL, 3.1 equiv) in anhydrous THF (115 mL; -80°C, nitrogen) was added dropwise while stirring a 2.5 M solution of *n*-butyllithium in hexanes (12 mL, 2.25 equiv). After 1 hour at -80°C, a solution of **3b** (2.23 g, 13.2 mmol) in THF (12 mL) was added. After 45 additional min at -80°C, the reaction mixture was quenched with 25% aqueous ammonium acetate. Extractive isolation (ether) and purification by chromatography afforded **5b** (2.6 g, 79%) as an orange oil.
9. Acylation by N-methoxy-N-methylamides remarkably stopped at the ketone stage. On the other hand, the use of a more electrophilic reagent such as 3-(1-oxo-2-heptynyl)-2-thiazolidinethione resulted in a double addition leading to a tertiary alcohol. Several attempted preparations of 2-heptynoyl acid chloride invariably resulted in concomitant partial addition of hydrogen chloride to the highly electrophilic triple bond.

10. A similar protocol was used to that previously described with a β-keto phosphonate in methanol instead of aqueous THF.[17]
11. Another attempted route first involving acylation of **4** via its α-lithio derivative by N-methoxy-N-methyl-2-propynamide proved unsuccessful. A low (13%) and unreliable yield of 1-(5-(1,3-dioxolan-2-yl)-2-furanyl)-2-propyn-1-one resulted. Furthermore, palladium-catalyzed coupling of this monosubstituted alkyne with (Z)-1-iodo-1-butene under the conditions previously reported failed to give any desired enyne **5a**.
12. For another synthesis of this compound see Einhorn, J.; Einhorn, C.; Luche, J-L. *Synth. Commun.* **1990**, *20*, 1105 - 1112.
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14. (4*Z*)-N-Methoxy-N-methyl-4-hepten-2-ynamide **3a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.21 (dt, 1H, J = 10.8, 7.5 Hz, CH=C<u>H</u>-CH_2), 5.58 (dt, 1H, J = 10.8, 1.4 Hz, C<u>H</u>=CH-CH_2), 3.79 (s, 3H, O<u>C</u>H_3), 3.27 (broad s, 3H, N<u>C</u>H_3), 2.40 (qdd, 2H, J = 7.6, 7.5, 1.2 Hz, <u>C</u>H_2CH_3), 1.05 (t, 3H, J = 7.6 Hz, <u>C</u>H_3); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ 154.21 (<u>C</u>O), 151.26 (CH=<u>C</u>H-Et), 106.67 (<u>C</u>H=CH-Et), 87.42 (CO-C≡<u>C</u>), 85.01 (CO-<u>C</u>≡C), 61.89 (O<u>C</u>H_3), 32.96 (N<u>C</u>H_3), 24.28 (<u>C</u>H_2CH_3), 13.21 (<u>C</u>H_3).
15. Wyerone **1a** : m.p.: 63.5°C (lit.,[3] 63 - 64°C); ^{1}H NMR ($CDCl_3$, 90 MHz) δ 7.46 (d, 1H, J = 15.9 Hz, <u>C</u>H=CH-CO_2Me), 7.34 (d, 1H, J = 3.7 Hz, H-C_4 of furanyl), 6.74 (d, 1H, J = 3.7 Hz, H-C_3 of furanyl), 6.61 (d, 1H, J = 15.9 Hz, CH=<u>C</u>H-CO_2Me), 6.38 (dt, 1H, J = 10.8, 7.4 Hz, CH=C<u>H</u>-CH_2), 5.69 (dt, 1H, J = 10.8, 1.3 Hz, C<u>H</u>=CH-CH_2), 3.81 (s, 3H, O<u>C</u>H_3), 2.50 (qdd, 2H, J = 7.5, 7.4, 1.2 Hz, <u>C</u>H_2CH_3), 1.11 (t, 3H, J = 7.5 Hz, <u>C</u>H_3); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ 166.46 (<u>C</u>O_2Me), 164.49 (<u>C</u>O ketone), 154.83 (C_2 of furanyl e. g. α to C=C), 153.94 (CH=<u>C</u>H-Et), 153.62 (C_5 of furanyl e. g. α to CO ketone), 130.01 (<u>C</u>H=CH-CO_2Me), 121.38 (C_4 of fura-nyl), 120.70 (CH=<u>C</u>H-CO_2Me), 115.84 (C_3 of furanyl), 106.41 (<u>C</u>H=CH-Et), 90.60 (CO-<u>C</u>≡C), 89.87 (CO-C≡<u>C</u>), 51.93 (O<u>C</u>H_3), 24.73 (<u>C</u>H_2CH_3), 13.14 (<u>C</u>H_3).
Z-isomer of wyerone : m.p.: 66°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.81 (d, 1H, J = 3.9 Hz, H-C_4 of furanyl), 7.37 (dd, 1H, J = 3.8, 0.4 Hz, H-C_3 of furanyl), 6.86 (d, 1H, J = 13.0 Hz, <u>C</u>H=CH-CO_2Me), 6.35 (dt, 1H, J = 10.8, 7.5 Hz, CH=C<u>H</u>-CH_2), 6.03 (d, 1H, J = 13.0 Hz, CH=<u>C</u>H-CO_2Me), 5.68 (dt, 1H, J = 10.8, 1.4 Hz, <u>C</u>H=CH-CH_2), 3.80 (s, 3H, O<u>C</u>H_3), 2.48 (qdd, 2H, J = 7.5, 7.5, 1.4 Hz, <u>C</u>H_2CH_3), 1.10 (t, 3H, J = 7.5 Hz, <u>C</u>H_3); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ 165.68 (<u>C</u>O_2Me), 164.53 (<u>C</u>O ketone), 154.52 (C_2 of furanyl e. g. α to C=C), 153.65 (CH=<u>C</u>H-Et), 152.63 (C_5 of furanyl e. g. α to CO ketone), 129.38 (<u>C</u>H=CH-CO_2Me), 122.15 (C_4 of furanyl), 119.99 (CH=<u>C</u>H-CO_2Me), 118.37 (C_3 of furanyl), 106.44 (<u>C</u>H=CH-Et), 90.69 (CO-<u>C</u>≡C), 89.50 (CO-C≡<u>C</u>), 51.67 (O<u>C</u>H_3), 24.66 (<u>C</u>H_2CH_3), 13.18 (<u>C</u>H_3).
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