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Communications

Study toward the Total Synthesis of Forskolin (I) Synthesis of the Trien 13 as a Key Intermediate Utilizing KF-Alumina Mediated Alkylation

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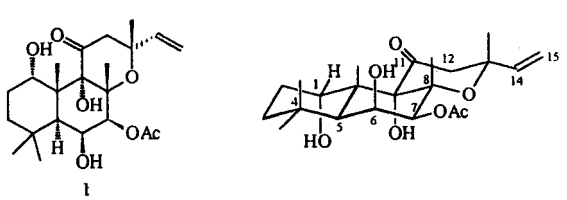
The forskolin **1** is a diterpene obtained from the roots of *Coleus forskohlii* (Willd.)[1] Brig., (*Lamiaceae*) which has been described in Ayurvedic materia medica and in ancient Hindu medicinal texts as a remedy for several complaints, including heart diseases and central nervous system (CNS) disorders such as insomnia and convulsions. The absolute structure of it was determined from the crude methanolic extract of *Coleus forsolii* in 1977 by the research group at Hoechest (Figure 1).[1,2] Later, it has been found a strong positive inotropic effect on the heart muscle[3] and to be an antihypertensive. In clinical studies, forskolin **1** has shown promising potential as a novel drug for the treatment of diseases such as glaucoma, congestive heart failure,[4] and bronchial asthma.[5] Forskolin derivatives which had the same carbon skeleton with different functional groups were reported.[2,6] They have eight chiral centers and various oxygenated functional groups -hydroxyl, acetate, ketone- with an ether linkage in their tricylic carbon skeleton. They have attracted considerable interests for synthetic chemists[7] because of their unique structure and biological activities. The total synthesis of forskolin **1** was reported by Ziegler[8a] followed by Corey[8b] and Ikegami.[8c] The formal synthesis for the key intermediate -Ziegler intermediate **2** (Figure 2)- was reported by several others.[9] However, all of these synthetic routes required more than 20 steps in order to build the carbon skeleton with the necessary functional groups.



1

Forskolin

Figure 1.

We have investigated a conceptually different approach utilizing the cationic polyene cyclization.[10] Our retrosynthetic analysis is depicted in Scheme 1. Forskolin **1** and its analogues would be synthesized from the key intermediate **4**. The tetramethyl hexahydrobenzochromone of **4** would be constructed from the substrate **5** by the cationic triene cyclization reaction. The triene substrate **5** could be prepared by coupling reaction between the compound **6** and **7**. Herein we report the synthesis of the compound **5** as a key intermediate for total synthesis of forskolin (Scheme 2).

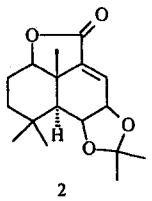


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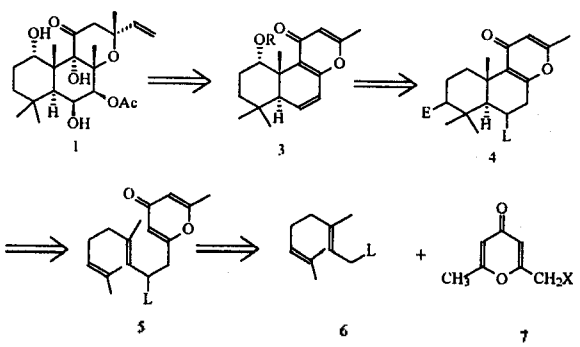
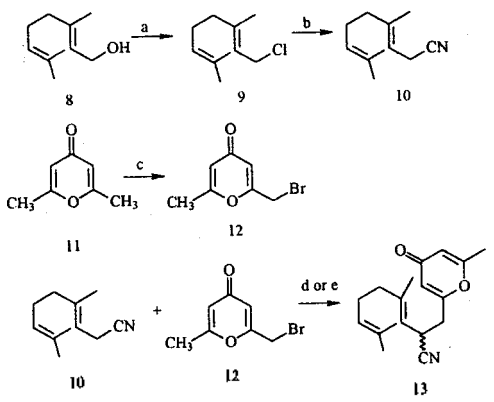
Figure 2.



Scheme 1.



Scheme 2.

For the present purpose, we prepared (E)-4,8-dimethyl-3,7-nonadienenitrile **10** from geraniol **8**. Geranyl chloride **9**[11] was obtained by treatment of geraniol **8** with 2.00 equivalent of LiCl, 1.60 equivalent of mesyl chloride and 1.60 equivalent of 2,4,6-collidine in DMF at 0 ℃ for 3 hr. The reaction was completed under the mild condition without isolation of the intermediate (mesylate). Isolation of the mesylate is not recommended since it is very labile. Displacement of the chloride by the cyanide utilizing potassium cyanide in DMSO below at 25 ℃ gave the product (E)-4,8-dimethyl-3,7-nonadienenitrile **10** in 72.0% yield. Heating above 25 ℃ or prolonging the reaction time over 12 hours caused the significant lower yield.

The 2-(bromomethyl-6-methyl)-4H-pyran-4-one **12**, has been synthesized by the modified literature procedure. In our laboratory, the yield of selective monobromination of 6-dimethyl-γ-pyrone **11** could be increased from 19.6% (literature value)[12] up to 45.6% based on recovering starting material (about 20%) by the careful control of the addition mode and amount of reagents (benzoylperoxide as an initiator and N-bromosuccinimide as a bromine source). In addition, dilution of reaction mixture also led to a significant increase in yield since the low solubility of 2,6-dimethy-γ-pyrone **2** in organic solvents.

Treatment with (E)-4, 8-dimethyl-3,7-nonadienenitrile **10** with LDA followed by the addition of the bromopyrone **12** gave the triene **13** in low yield (17.6%). The various reaction conditions- different bases, solvents and additives- were tried but did not give the significant improvement. Under our conditions, the unchanged nitrile **10** was recovered even though the bromopyrone **12** was completely disappeared on TLC. We believed that the cabanion at C-2 on the nitrile **10** was not reactive enough to be a nucleophile since the homoallylic interaction between the nitrile and the methyl group at C-4 broke the coplanity of π-bond of the vinyl group and the nitrile.[13]

In order to circumvent the low yield reaction, we employed potassium fluoride on alumina chemistry[14] which was used in our laboratory for other synthesis.[15] Alumina coated with potassium fluoride proved to be a versatile solid base for olefine and acetylene forming elimination, the Michael addition, aldol condensation, and the Darzens condensation. However, the detailed mechanistic study has not been reported so far. When potassium fluoride on alumina condition was employed at room temperature, the yield of **13** was improved up to 32.0% yield (Scheme 2). with the recovered starting nitrile (30.5%). According to our observations, the hydroxide ion generated from potassium fluoride on alumina works as an efficient base for our system. But more experimental data are required to confirm our interpretation. The application of KF-alumina to other carbon skeleton is under investingation in our laboratory.

In summary, the key intermediate **13** was readily synthesized from a geraniol **8** for 4 steps by a convergent manner utilizing potassium fluoride on alumina mediated alkylation as a key step. The study of the cationic polygene cyclization is currently in progress and will be reported.

Acknowledgments. we are grateful to the Basic Science Research Institute Program (Project No. 3417, 1995) by the Ministry of Education and thank the Organic Chemistry Research Center in Sogang University for the elementary analysis.

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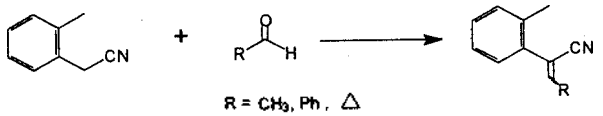
15. The following transformation was successfully acheived by untilizing KF-alumina in our laboratory.



16. All compounds were isolated and fully characterized by spectroscopic methods. For example: Compound **10** ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.20 (t, 1H, J=6.9), 5.10 (m, 1H), 3.07 (d, 2H, J=6.9), 2.08 (m, 4H), 1.69 (s, 3H), 1.68 (s, 3H), 1.62 (s, 3H) Compound **13** ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.11 (s, 1H), 6.09 (s, 1H), 5.10 (t, 1H), 5.34 (m, 1H, J=8.8), 3.38 (ddd, 1H, J=8.8, 7.6, 7.4), 2.91 (ABq, 1H, J=7.4, 7.2), 2.73 (ABq, 1H, J=7.6, 7.2), 2.26 (s, 3H), 2.04 (m, 4H), 1.66 (s, 3H), 1.66 (s, 3H), 1.58 (s, 3H).

Oxidation of Aromatic Ketone Hydrazones by Thianthrene Cation Radical

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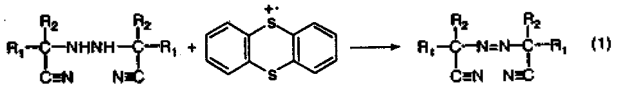
Recently we have reported the efficient, cation radical-induced, oxidation of hydrazonitriles to the corresponding azo compounds (eq 1).[1] But an unstable azoalkane, 3,6-dicyano-3,6-dimethyl-1,2-diazacyclohexene, decomposed to give the cleavage product, methacrylonitrile and the coupled product, trans-1,2-dicyano-1,2-dimethylcyclobutane with nitrogen evolution. With the view of increasing the scope of this cation radical-induced oxidation, we successfully investigated the transformation of aromatic ketone hydrazones into diazo compounds.



We now report a new oxidation of four unsubstituted aromatic ketone hydrazones induced by thianthreniumyl perchlorate ($Th^{+}\cdot ClO_4^-$): bezophenone hydrazone **1**, 9-fluorenone hydrazone **2**, benzil monohydrazone **3**, and benzil dihydrazone **4**.

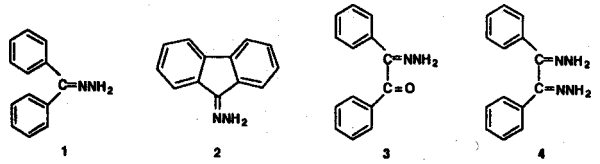


Table 1. Oxidation of Ketone Hydrazones to Diazo Compounds by Thianthrene Cation Radical[a]

Run	Ketone hydrazone[b]	Yields (%)[b] 7	8	9	12	Th	ThO
1	**1**	94				90	2
2	**2**		75			80	4
3	**3**			80		83	2
4[c]	**4**				74	86	7

[a] Oxidation was carried out by general procedure. Solid $Th^{+}\cdot ClO_4^-$ and ketone hydrazone in the mole ratio 2 : 1 were placed under argon in a septum-capped flask into which 20 mL of acetonitrile was injected by syringe. The dark purple color of $Th^{+}\cdot$ disappeared with time, but the solution was stirred overnight. Water (5 mL) was then added, the solution was neutralized with $NaHCO_3$ and extracted repeatedly with CH_2Cl_2 (4×20 mL) and the dried CH_2Cl_2 solution was evaporated. The residue thus obtained was taken up in a standard volume of CH_2Cl_2, and the solution was analyzed. [b] Each reaction was run twice, and the averaged yiels of products are given. Products were identified and quantified by GC, using the method of "standard addition" of authentic samples,[19] and by ^{1}H NMR and GC/MS. GC analysis employed a 2 m×1/8 in. 10% OV-101/Chrom W packed column programmed from 50 to 250° at 10 deg/min. The ketone hydrazones and the four products were prepared by standard procedures as referenced and had satisfactory GC/MS, NMR, and other data. [c] The mole ratio of cation radical to **4** was 4 : 1.

The oxidation of ketone hydrazones and vicinal dihydrazones has wide applications as a fundamental reaction in diazoalkane synthesis[2,3] using mercuric oxide as dominant oxidizing reagent. For example, while aromatic ketone hydrazones **1**[2,4] and **2**[5] are transformed into the corresponding diazo compounds, benzil monohydrazone **3** yields α-diazoketone[6~8] and dihydrazone **4** is converted into diphenylacetylene **12**.[9,10]

While $Th^{+}\cdot$ was reduced quantitatively to thianthrene (Th), the diazo compounds, diazodiphenylmethane **7**, 9-diazofluorene **8**, and phenylbenzoyl diazomethane **9** were produced in good yields by the oxidation of **1**, **2**, and **3**. Results are given in Table 1. The mechanism for the formation of $Ar_2C{=}N_2$ is shown in Scheme 1, although we do not have sufficient knowledge of the mechanistic details to establish the sequence of steps shown with $Th^{+}\cdot$ as oxidant. Route (a) in Scheme 1 is a net electron transfer reaction and deprotonation steps occuring by basic nitrile solvents. Route (b) shows that $Th^{+}\cdot$ bonds to the nitrogen atom of the hydrazone. We favor the second route since it is analogous to the reactions of $Th^{+}\cdot$ with aryl aldehyde oximes,[11] and with hydrazonitriles.[1] In those reactions, $Th^{+}\cdot$ bonds to the nitrogen atom of aldoxime produced aldehyde[11] and bonds to the nitrogen atom of hydrazonitrile produced an azo compound.[1] In route (b) on Scheme 1, the formation of the diazo compound may originate from intermediates **5** and **6** resulting from attack of $Th^{+}\cdot$ on the nitrogen atom of ketone hydrazone. Reactions between ammonia, or primary and secondary alkylamines, and the sulfur atom in $Th^{+}\cdot$ and analogous cation radicals have been reported and may serve as precedents for favoring the route (b) mechanism.[12,13]

Bezophenone hydrazone **1** reacted rapidly with $Th^{+}\cdot ClO_4^-$