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Direct Synthesis of 2-Substituted Furotropones from Tropolones Utilizing Alkynyl(phenyl)iodonium Salts

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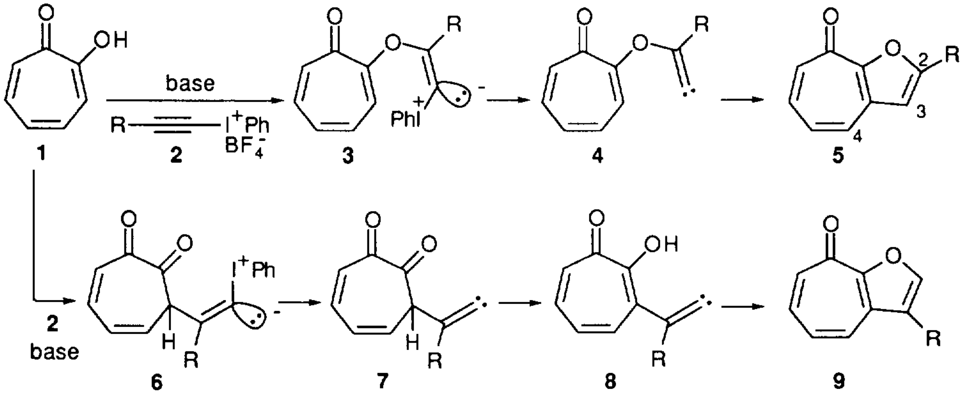
Abstract: Reaction of alkynyl(phenyl)iodonium tetrafluoroborates with tropolones in the presence of a base undergoes tandem *O*-Michael-carbene insertions and provides a useful route for the direct synthesis of 2-substituted furotropones from tropolones. Copyright © 1996 Elsevier Science Ltd

Alkynyl(phenyl)iodonium salts undergo Michael-type addition of a variety of soft nucleophiles including stable enolates of 1,3-dicarbonyl compounds, oxygen nucleophiles (carboxylates and phenoxides), and sulfur nucleophiles (sulfinates and thiocyanates) yielding iodonium ylides, which generate alkylidenecarbenes through reductive elimination of iodobenzene.[1] Enolate anions of carbonyl compounds bearing two reactive sites generally act as a carbon nucleophile and not as an oxygen nucleophile in this Michael-type reaction toward the alkynyliodonium salts.[2]

Tropolones and their anions appear to function similarly to enolates as ambident nucleophiles.[3] For instance, methylation of the potassium salt of tropolone **1** with methyl iodide in the presence of dicyclohexyl-18-crown-6 takes place at the oxygen atom yielding tropolone methyl ether selectively,[4] while both electrophilic bromination and iodination of **1** proceed at the 3-position because of the cyclic vinylogous nature of 1,3-dicarbonyl compounds.[5] Therefore, in the reaction of tropolonate anions with alkynyliodonium salts **2**, two



a; R = Me, **b**; R = n-C_8H_{17}, **c**, R = $(CH_2)_2CHMe_2$, **d**; R = $(CH_2)_2Ph$, **e**; R = $(CH_2)_3Ph$, **f**; R = CH_2-*cyclo*-C_5H_9, **g**; R = i-Pr, **h**; R = t-Bu

Scheme 1

types of Michael additions to the β-acetylenic carbon of **2** seem to be possible (Scheme 1): 1) Michael-type addition of the tropolonate anion as an oxygen nucleophile generating α-oxyalkylidenecarbenes **4** (*O*-Michael addition), 2) Michael-type addition as a carbon nucleophile generating hydroxyalkylidenecarbenes **8** via 1,3-shift of hydrogen of α-diketones **7** (*C*-Michael addition). We report herein a reaction of alkynyliodonium salts **2** with anions of tropolones, which, in contrast to the reaction with enolates, proceeds exclusively through *O*-Michael addition. The reaction makes possible a direct synthesis of furotropones from tropolones by way of tandem Michael-carbene insertion reactions.

Reaction of the potassium salt of tropolone **1**, generated by the reaction with *t*-BuOK at room temperature, with 1-decynyl(phenyl)iodonium tetrafluoroborate **2b** (1.2 equiv.) in dichloromethane at room temperature for 15 h under argon afforded the furotropone 2-octyl-8*H*-cyclohepta[*b*]furan-8-one **5b** in 36% yield, along with the formation of tropolone 2-oxodecyl ether (11%) and 1-iodo-1-decyne (29%).[6,7] A variety of solvents including benzene, tetrahydrofuran (THF), and hexamethylphosphoric triamide (HMPA) are useful in this reaction; especially, more than 60% yield of the furotropone **5b** was obtained by using a mixed solvent benzene-HMPA (4:1). The structure of **5b** and tropolone 2-oxodecyl ether was determined by spectroscopy using two-dimensional (2D) NMR techniques, i.e., ^{1}H,^{1}H-, and ^{13}C,^{1}H-COSY and nuclear Overhauser enhancement spectroscopy (NOESY), and mass spectrometry. Observation of NOE between C_3-H and C_4-H firmly established the 2-alkyl-substituted structure of **5b**; the alternative regioisomer of furotropone **9b** with 3-octyl substituent is not compatible with this result.

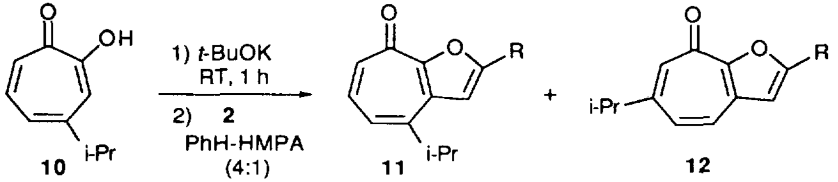
This direct method for the synthesis of 2-substituted furotropones **5** was applied to a variety of alkynyliodonium salts **2a-h**[8] and the results are summarized in Table 1. A 4:1 mixture of benzene-HMPA was used as the solvent; however, the reaction of 1-propynyliodonium salt **2a** was carried out in THF, since 2-methylfurotropone **5a**[9,10] is highly soluble in water owing to the hydrogen bonding, which makes the isolation of **5a** from the reaction mixture in the presence of HMPA very difficult. The reaction of 3,3-dimethyl-1-butynyliodonium salt **2h** is very slow: even after heating the reaction mixture in benzene at 50 °C for 8 days, some starting materials **1** and **2h** still remain unchanged (Table 1, Entry 8). The sterically demanding bulky *t*-butyl group of **2h** would retard the Michael addition of the tropolonate anion.

Table 1 Direct Synthesis of Furotropone **5** from Tropolone **1** by the Reaction with **2**[a]

Entry	2	Solvent	Conditions	5	Yield[b]/%
1	**2a**	THF	RT, 42 h	**5a**	42[c]
2	**2b**	PhH-HMPA(4:1)	RT, 7 h	**5b**	64
3	**2c**	PhH-HMPA(4:1)	RT, 5 h	**5c**	53
4	**2d**	PhH-HMPA(4:1)	RT, 18 h	**5d**	45
5	**2e**	PhH-HMPA(4:1)	RT, 5 h	**5e**	48
6	**2f**	PhH-HMPA(4:1)	RT, 5 h	**5f**	62
7	**2g**	PhH-HMPA(4:1)	RT, 5 h	**5g**	58
8	**2h**	PhH	50 °C, 8 d	**5h**	54

[a] Reactions were carried out using *t*-BuOK under argon. [b] Isolated yields. [c] Tropolone 2-oxopropyl ether was isolated in 11% yield and the structure was determined by comparison with the authentic sample, prepared from the reaction of **1** with 1-bromo-2-propanone in the presence of K_2CO_3.

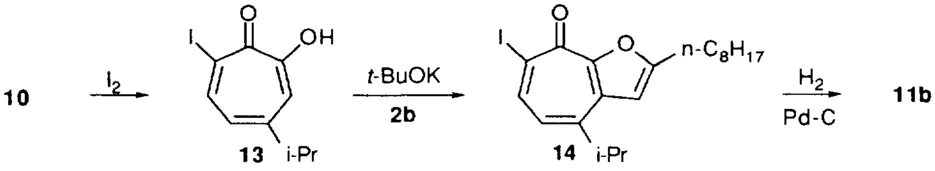
Table 2 Reaction of Hinokitiol **10** with Alkynyliodonium Salts **2**



Entry	2	Conditions	Product (11 and 12)	
			Yield[a]/%	Ratio (11:12)
1	**2b**[b]	RT, 2 h	65	51:49
2	**2c**	RT, 5 h	60	51:49
3	**2e**	RT, 5 h	42	48:52
4	**2f**	RT, 5 h	59	45:55
5	**2g**	RT, 5 h	59	49:51

[a] Isolated total yields. [b] THF-HMPA (4:1) was used as the solvent.

A regioisomeric mixture of furotropones was obtained in the reaction of hinokitiol **10** (Table 2); for instance, reaction with **2b** afforded a 65% yield of 1:1 mixture of the 4-isopropyl-2-octylfurotropone **11b** and the 6-isopropyl isomer **12b**. The structure of these regioisomers was determined by ^{1}H NMR spectra in C_6D_6: C_7-H of **11b** appeared at δ 7.18 as a doublet (*J* 12.5 Hz), while that of **12b** at δ 7.31 as a singlet. The introduction of iodine at C_7 of hinokitiol **10** makes the selective synthesis of **11b** possible (Scheme 2): regioselective iodination of **10** yielding **13** (70%),[4b] followed by treatment of its potassium salt with **2b**, gave 7-iodofurotropone **14** (43%), which, on reduction using 5% Pd-C in hydrogen, afforded **11b** (99%).



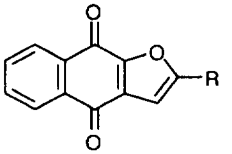
Scheme 2

C-Michael addition mechanism of potassium tropolonate to the alkynyliodonium salts **2** generating hydroxyalkylidenecarbenes **8**, which is a reported general reaction pathway of enolate anions of 1,3-dicarbonyl compounds,[2] is not compatible with the formation of 2-substituted furotropones **5**. This process will generate *cisoid* 1,2-dioxovinyliodonium ylide **6**, which most probably suffers not only an unfavorable dipole-dipole interaction of the carbonyl groups but also a decrease in delocalization energies.[11] Therefore, an alternative *O*-Michael addition would become a preferred process, generating α-oxyalkylidenecarbenes **4** through reductive elimination of iodobenzene from the resulting vinyliodonium ylide **3**.

Intramolecular 1,5-carbon-hydrogen insertion of alkylidenecarbenes to C_{sp2}-H bonds has been shown to be difficult, presumably because of the higher bond energy than that of C_{sp3}-H bonds.[12,13] However, the predominant formation of furotropones **5b**, **5c**, **5e**, and **5f** clearly indicates the high selectivity for insertion of α-oxyalkylidenecarbene **4** to the vinylic C-H over the aliphatic C-H bonds. As was suggested by Taniguchi and

Kitamura,[14] the marked selectivity of vinylic 1,5-C-H insertion is most probably a result of the presence of the α-oxygen atom of the alkylidenecarbene **4**.

The method developed here makes possible the direct synthesis of furanonaphthoquinones **15**, some of which show antileukemic activity:[15] exposure of the potassium salt of 2-hydroxy-1,4-naphthoquinone to alkynyliodonium salts **2b** and **2f** undergoes the tandem Michael-carbene insertions yielding **15a** (32%) and **15b** (41%), respectively.



15a; R = *n*-C_8H_{17}
15b; R = CH_2-*cyclo*-C_5H_9

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7. All new compounds were fully characterized by spectroscopic means and/or elemental analyses. Selected spectroscopic data for **5b**: IR ($CHCl_3$) 2920, 2850, 1630, 1580, 1545, 1480, 1155 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 7.19 (br d, *J* = 12.4 Hz, 1H), 6.73 (br d, *J* = 10.7 Hz, 1H), 6.54 (br dd, *J* = 12.4, 8.5 Hz, 1H), 6.26 (br dd, *J* = 10.7, 8.5 Hz, 1H), 5.89 (s, 1H), 2.39 (t, *J* = 7.2 Hz, 2H), 1.46 (quint, *J* = 7.2 Hz, 2H), 1.34-1.06 (m, 10H), 0.91 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (C_6D_6, 100 MHz) δ 174.1 (s), 162.3 (s), 156.1 (s), 139.4 (d), 134.2 (d), 131.7 (s), 129.2 (d), 127.7 (d), 108.6 (d), 32.2 (t), 29.5 (t), 29.4 (t), 28.2 (t), 27.7 (t), 23.0 (t), 14.3 (q); MS *m/z* (relative intensity) 258 (51, M^+), 229 (12), 215 (14), 187 (23), 174 (19), 174 (100), 160 (42), 131 (42), 77 (11); HRMS Calcd for $C_{17}H_{22}O_2$ (M^+) 258.1620. Found 258.1617.
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