Gold(III) Bromide Catalyzed Furannulation of 2-Alkynylcycloalk-2-enols: An Expedient Route to Fused Furans

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Abstract: An efficient synthesis of fused furans from 2-alkynylcycloalk-2-enols via gold(III) bromide catalyzed cycloisomerization was achieved. The reaction condition is moderate and amenable to structurally diverse substrates, leading to good yield of products.

Key words: 2-alkynylcycloalk-2-enol, gold(III), cycloisomerization, fused furans

Fused furans are important heterocyclic target molecules because of their occurrence as structural units in a variety of natural products and biologically active compounds[1] (Figure 1). These includes tubipofurane (**1**) an *ent*-furanoeudesmane, isolated from the stolonifier *Tubipora musica*, shows ichtiotoxicity toward a killifish *Orizias latipes*.[2] Pallescensin A (**2**), obtained from the marine sponge *Disidea Pallescens* involves in the defensive mechanism employed by opisthobranch molluscs, which concentrate such sponge metabolites in their skin and then release them when they come under attack.[3]

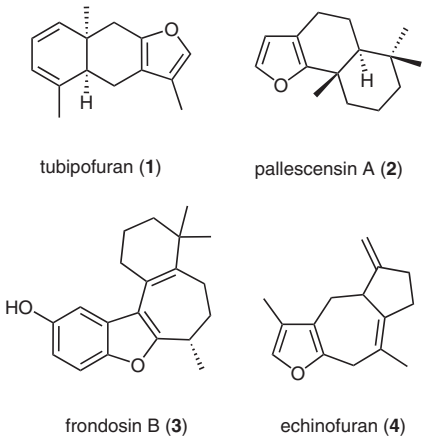
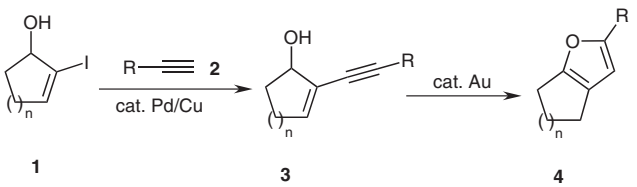


Figure 1 Examples of naturally occurring fused furans

Frondosin B (**3**), isolated from a marine sponge *Dysidea frondosa* was shown to possess interleukin-8 (IL-8) inhibitory activity.[4] Echinofuran (**4**), a kind of furanosesquiterpenoid-tetrahydrolinderazulene isolated from the gorgonian species *Echinogorgia praelonga* was found to inhibit the cell division of fertilized sea urchin eggs.[5] A number of natural products and their metabolites possessing fused furan rings continues to emerge in the literature.[1e,f] Therefore the synthesis of these structural motifs receives paramount importance in synthetic viewpoint. Not surprisingly, many synthetic approaches to this skeleton have been disclosed in the literature.[6] Of particular value are Pt(II)-catalyzed cyclization of propargyl oxiranes,[6a] Au(III)-,[6b] Pt(II)-,[6c] and Cu(I)[6d]-catalyzed cyclization of 2-(1-alkynyl)-2-alken-1-ones in the presence of alcohol, Au(I)-catalyzed ring expansion of 1-alkynylbicyclo[4.1.0]heptan-2-ones,[6e] intramolecular condensation of triketones promoted by trimethylsilylchloride under microwave irradiation.[6f] Apart from these methodologies, there have been many strategies disclosed in the literature for the construction of fused furan-containing natural products.[1d,h,2b,4a,5a,7] Despite the conceivable synthetic utility of the above methodologies, a catalytic protocol accomplishing the furannulation of 2-alkynylcycloalk-2-enol remains to be developed. On the other hand, because of their unique ability to activate carbon–carbon triple bond, the use of gold catalysts plays an important role in modern transition-metal catalysis.[8] Moreover, gold catalysts have proved to be very efficient in intramolecular cyclization of acetylenic alcohols to the corresponding oxygenated heterocycles.[9] As part of our ongoing interest directed towards the synthetic applications of gold catalysts,[10] we planned to investigate the catalytic cycloisomerization of 2-alkynylcycloalk-2-enol in the presence of a gold salt. Although cycloisomerization of 2-alkynyl-3-alkyl allyl alcohol using $AgNO_3$,[11] $Pd(MeCN)_2Cl_2$,[12] to furans have been already reported, there have been no precedents for the cycloisomerization of 2-alkynylcycloalk-2-enol, leading to fused furans. Therefore a two-step approach to fused furans has been examined involving (i) the Sonogashira coupling[13] of 2-iodocycloalk-2-enol with terminal alkynes and (ii) gold-catalyzed cycloisomerization (Scheme 1). Herein, we report a more convenient synthesis of the starting 2-alkynylcycloalk-2-enols and the successful application of gold(III)-catalyzed cycloisomerization strategy as a convenient and general synthetic method for the synthesis of fused furans.



Scheme 1 Synthetic strategy for fused furans

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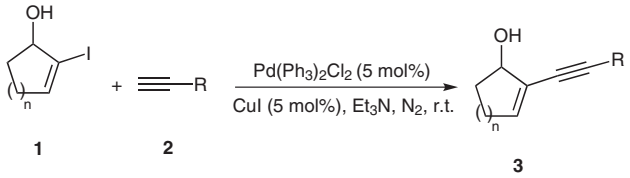
Table 1 Synthesis of 2-Alkynylcycloalk-2-enol under Sonogashira Conditions[a]



1 **2** **3**

a n = 3, **b** n = 2, **c** n = 1

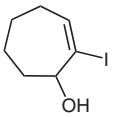
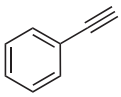
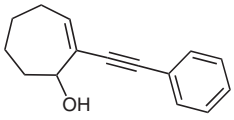
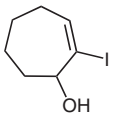
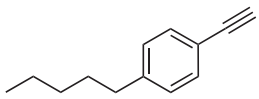
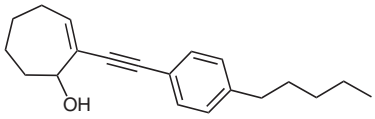
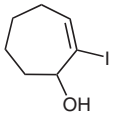
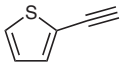
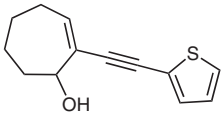
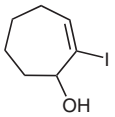
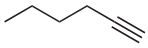
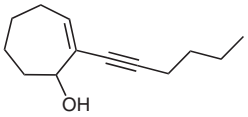
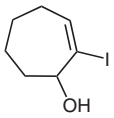
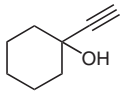
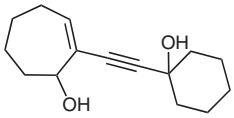
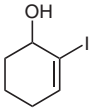
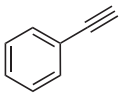
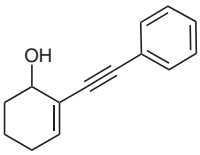
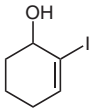
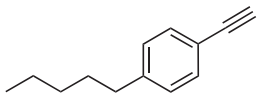
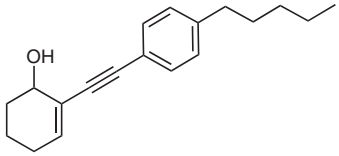
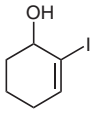
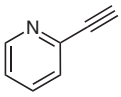
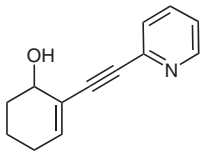
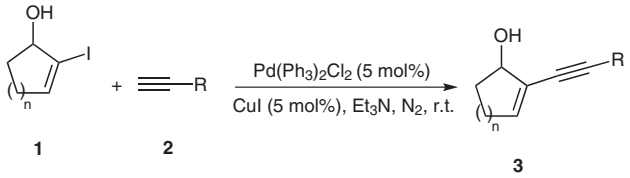
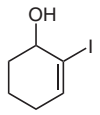
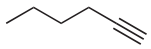
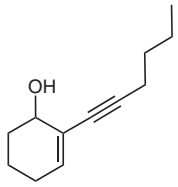
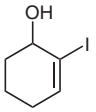
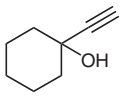
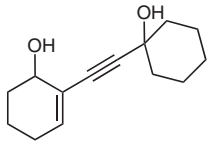
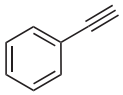
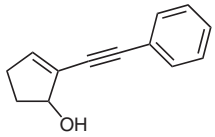
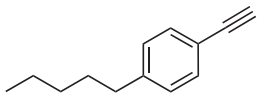
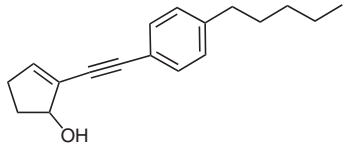
Entry	2-Iodocycloalk-2-enol (**1**)	Alkyne (**2**)	2-Alkynyl-1-cycloalk-2-enol (**3**)[b]	Yield (%)[c]
1	 **1a**	 **2a**	 **3a**	90
2	 **1a**	 **2b**	 **3b**	92
3	 **1a**	 **2c**	 **3c**	88
4	 **1a**	 **2d**	 **3d**	89
5	 **1a**	 **2e**	 **3e**	77
6	 **1b**	 **2a**	 **3f**	91
7	 **1b**	 **2b**	 **3g**	94
8	 **1b**	 **2f**	 **3h**	79

Table 1 Synthesis of 2-Alkynylcycloalk-2-enol under Sonogashira Conditions[a] (continued)



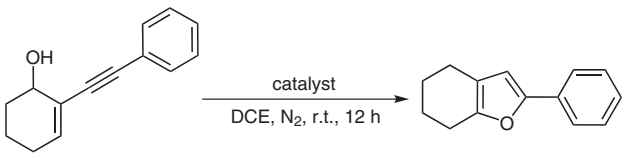
1 **2** **3**

a n = 3, **b** n = 2, **c** n = 1

Entry	2-Iodocycloalk-2-enol (**1**)	Alkyne (**2**)	2-Alkynyl-1-cycloalk-2-enol (**3**)[b]	Yield (%)[c]
9	 **1b**	 **2d**	 **3i**	89
10	 **1b**	 **2e**	 **3j**	79
11	 **1c**	 **2a**	 **3k**	80
12	 **1c**	 **2b**	 **3l**	81

[a] All reactions were carried out at r.t. for 6 h using of 2-iodocycloalk-2-enol (1.0 mmol), terminal alkyne (1.2 mmol), $Pd(PPh_3)_2Cl_2$ (5 mol%) and CuI (5 mol%), respectively, in dry Et_3N (5 mL) under a nitrogen atmosphere.
[b] All products were characterized by IR, ^1H NMR, ^{13}C NMR, and MS.
[c] Isolated yield.

To assess the generality of this approach, the scope of the Sonogashira coupling of 2-iodocycloalk-2-enols and terminal alkynes were first studied. Treatment of 2-iodocycloalk-2-enols **1** with a variety of terminal alkynes under standard Sonogashira conditions [1.0 mmol of 2-iodocycloalk-2-enol, 1.2 mmol of terminal alkyne, 5 mol% of $Pd(Ph_3)_2Cl_2$, 5 mol% of CuI and 5 mL of Et_3N at r.t. for 6 h] affords good to excellent yields of the coupling products (Table 1 and Table 2).[14]



3f **4f**

Scheme 2

Initial studies were conducted using 2-(phenylethynyl)-cyclohex-2-enol (**3f**) as a prototype reaction in dichloroethane at room temperature for 12 hours (Scheme 2). The use of AuCl led to a very low conversion of the starting material (Table 2, entry 1). Whereas, the use of gold (I) complexes, such as Ph_3PAuCl, Me_3PAuCl, and Et_3PAuCl did not lead to any desired product at all (Table 2, entries 2–4). However, the combination of gold(I) complex and AgOTf led to afford the product **4f** with increased yield (Table 2, entries 5 and 6). The use of AgOTf or $AuCl_3$ alone afforded the product in 25% yield only (Table 2, entries 7 and 8). Finally, the use of $AuBr_3$ gave the product in 55% yield (Table 2, entry 9). As 5 mol% of $AuBr_3$ gave the best result in terms of conversion and yield, it was used as the catalyst for our further studies. When the same reaction was carried out at elevated temperature (70 °C) using 5 mol% of $AuBr_3$, the reaction went into completion within 30 minutes and higher yield of the product (86%) was observed (Table 2, entry 10). So we followed the

Table 2 Effect of Different Gold Catalysts on the Cycloisomerization of 2-(Phenylethynyl)cyclohex-2-enol (**3f**)

Entry	Catalyst	Yield (%)[a]
1	AuCl (5 mol%)	12
2	Ph_3PAuCl (5 mol%)	trace
3	Me_3PAuCl (5 mol%)	–
4	Et_3PAuCl (5 mol%)	trace
5	Ph_3PAuCl (5 mol%)/AgOTf (5 mol%)	41
6	Et_3PAuCl (5 mol%)/AgOTf (5 mol%)	38
7	AgOTf (5 mol%)	25
8	$AuCl_3$ (5 mol%)	25
9	$AuBr_3$ (5 mol%)	55
10	$AuBr_3$ (5 mol%)	86[b]

[a] Isolated yield.
[b] The reaction was carried out at 70 °C for 30 min.

same reaction procedure for subsequent studies, which utilizes 5 mol% of $AuBr_3$ in dichloroethane at 70 °C.[15] Under this conditions, a wide variety of substrates bearing rings of different size, aromatic, aliphatic, and heteroaromatic groups have been successfully employed in this furan synthesis (Table 3). The results indicated that the efficiency of the cyclization depends on the nature of the size of the ring attached on the substrates (**3a**–**3l**). Substrates possessing cycloheptyl ring underwent the reaction at a short reaction time even at room temperature (Table 3, entries 1–5). Substrates owing cyclohexyl ring resulted in good yields of products only, when the reaction was carried out for 30 min at 70 °C (Table 3, entries 6–10). However, substrates having cyclopentyl rings gave the desired product, albeit in low yield even when the reaction was carried out for 45 minutes. These observations can be rationalized due to the greater strain associated with the formed cyclopenta[*b*]furan than cyclohexa[*b*]furan and cyclohept[*b*]furan. In contrast, the substituents on the triple bond of the 2-alkynylcycloalk-2-enol does not play a significant role in the cyclization, since groups like aliphatic, aromatic, and heteroaromatic gave almost the same yield of the product.

The formation of the products was ascertained by the appearance of a singlet peak at δ_H = 6.20–6.30 ppm in $CDCl_3$, which corresponds to the C3–H of the furan ring. Moreover all the products exhibited a ^{13}C peak at δ_C = 104–109 ppm, confirmed the presence of C3 carbon of the furan ring. On the basis of the above result, a mechanistic manifold for the formation of the fused furans is presented in Scheme 3. Thus, coordination of the carbophilic $AuBr_3$ to the alkyne **3** would lead to the formation of a π-complex **5**. As a consequence of the increased electrophilicity, a nucleophilic attack of the tethered hydroxyl group would lead to the cyclized intermediate **6**. Protodemetallation of **6**, followed by rearrangement would produce the fused furan **3**.

Table 3 Gold(III)-Catalyzed Synthesis of Fused Furans[a]

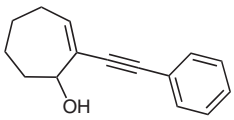
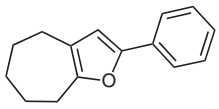
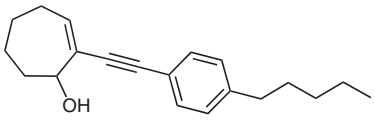
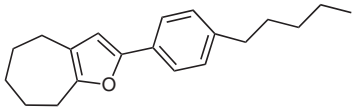
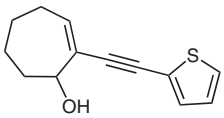
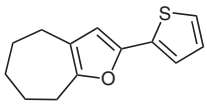
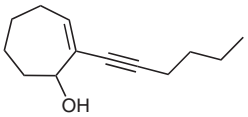
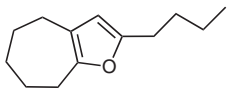
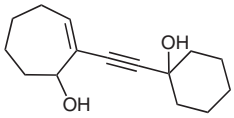
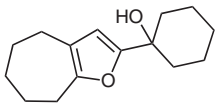
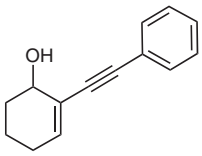
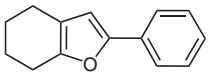
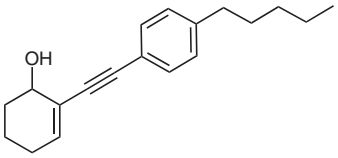
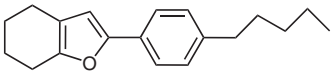
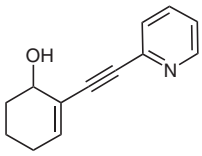
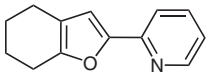
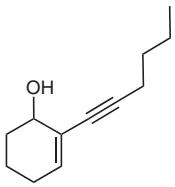
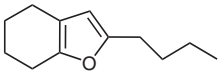
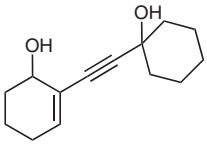
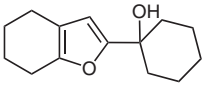
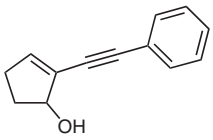
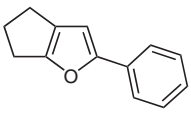
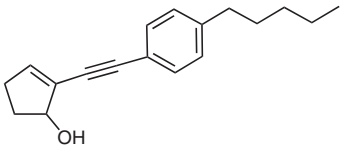
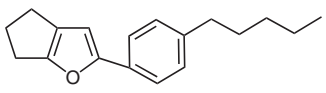
Entry	2-Alkynylcycloalk-2-enol (**3**)	Fused furan (**4**)[b]	Time (min)	Yield (%)[c]
1	 **3a**	 **4a**	2.0	90
2	 **3b**	 **4b**	1.0	91
3	 **3c**	 **4c**	1.0	89
4	 **3d**	 **4d**	4.0	95

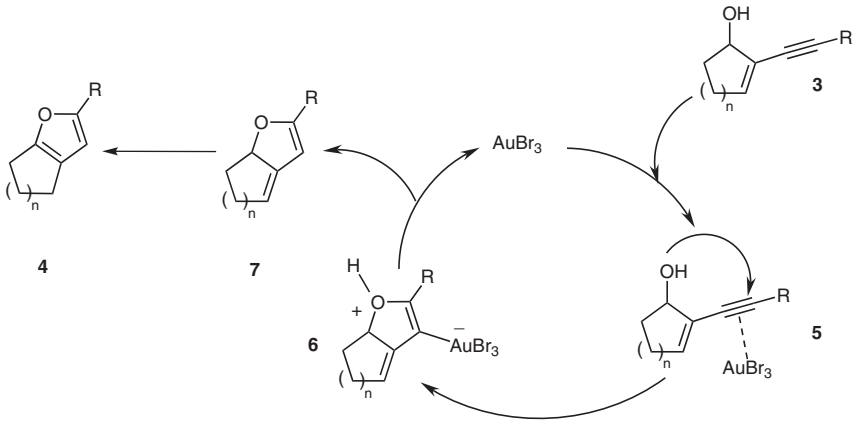
Table 3 Gold(III)-Catalyzed Synthesis of Fused Furans[a] (continued)

Entry	2-Alkynylcycloalk-2-enol (**3**)	Fused furan (**4**)[b]	Time (min)	Yield (%)[c]
5	 **3e**	 **4e**	5.0	79
6	 **3f**	 **4f**	30.0	86
7	 **3g**	 **4g**	30.0	88
8	 **3h**	 **4h**	30.0	70
9	 **3i**	 **4i**	30.0	92
10	 **3j**	 **4j**	30.0	83
11	 **3k**	 **4k**	45.0	60
12	 **3l**	 **4l**	45.0	66

[a] All reactions were carried out using $AuBr_3$ (5 mol%) in DCE. Reaction conditions: For substrates **3a–3e**, the reaction went to completion with in 5 min at 25 °C; for substrates **3f–j** the reactions were carried out at 70 °C for 30 min; for substrates **3k–l**, the reactions were carried out at 70 °C for 45 min.

[b] All products were characterized by IR, ^1H NMR, ^{13}C NMR, and MS.

[c] The yields were calculated after isolation from column chromatography.



Scheme 3 Proposed mechanism for the Au(III)-catalyzed cyloisomerization of 2-alkynylcycloalk-2-enol

In summary, we have developed an efficient synthesis of structurally diverse fused furans via Au(III)-catalyzed furannulation of 2-alkynylcycloalk-2-enols. The reaction conditions are simple, and the catalyst employed is very safe to use. Broad substrate scope and no additional solvent extraction steps are the other advantages of this method. Further studies to utilize this methodology for the synthesis of naturally occurring fused furans are actively under way.

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(14) **General Procedure for the Synthesis of 2-Alkynyl cyclo-alk-2-enol 3a–l**
Representative Procedure for 2-(Phenylethynyl)cyclohex-2-enol (3f, Table 1, Entry 6)
2-Iodocyclohex-2-enol (**1b**, 1.0 mmol), $Pd(PPh_3)Cl_2$ (5 mol%), and CuI (5 mol%) were placed in an oven-dried flask under N_2. Dry Et_3N was added, and the resulting suspension was magnetically stirred. Upon dropwise addition of phenylacetylene **2a** (1.2 mmol), the mixture was stirred at r.t. until TLC showed the disappearance of the starting 2-iodocyclohex-2-enol (ca. 6 h). H_2O (50 mL) was added to the reaction mixture, and the residue was extracted into EtOAc (4 × 15 mL), and the extract was dried over anhyd Na_2SO_4. Removal of the solvent under reduced pressure gave the crude product, which was further purified by column chromatography on silica gel using EtOAc–PE (1:9) as eluent to afford pure product **3f** (91%) as a brown oil. IR (CH_2Cl_2): 3383, 2928, 1592, 1053, 755 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.60–1.62 (m, 1 H), 1.75–1.78 (m, 3 H), 1.87–1.90 (m, 1 H), 2.12–2.21 (m, 2 H), 4.26 (br s, 1 H), 6.30 (t, *J* = 4.6 Hz, 1 H), 7.28–7.29 (m, 3 H), 7.43–7.44 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.1, 26.0, 30.6, 66.9, 88.4, 89.3, 123.2, 124.2, 128.2, 128.3, 131.6, 137.8. MS (EI): *m/z* = 198 [M^+]. Anal. Calcd for $C_{14}H_{14}O$: C, 84.81; H, 7.12. Found: C, 84.91; H, 7.09.

(15) **General Procedure for the Synthesis of Fused Furans 4a–l**
Representative Procedure for 2-Phenyl-4,5,6,7-tetrahydrobenzofuran (4f, Table 3, Entry 6)
To a soln of 2-(phenylethynyl)cyclohex-2-enol (**3f**, 1.0 mmol) in DCE (1 mL) under N_2 was added $AuBr_3$ (5 mol%) and heated the reaction mixture at 70 °C for 30 min. After completion of the reaction as indicated by TLC, the reaction mixture was concentrated under reduced pressure and purified by column chromatography over silica gel (100–200 mesh) to afford pure product **4f** (86%) as a colourless liquid. R_f = 0.82 (EtOAc–PE, 1:9). IR (CH_2Cl_2): 2934, 2815, 2354, 1669, 1600, 1247, 760 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.75–1.78 (m, 2 H), 1.84–1.89 (m, 2 H), 2.46 (t, *J* = 6.1 Hz, 2 H), 6.47 (s, 1 H), 7.20 (t, *J* = 7.6 Hz, 1 H), 7.35 (t, *J* = 7.6 Hz, 2 H), 7.62 (d, *J* = 6.9 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.2, 23.1, 23.2, 23.4, 106.1, 119.0, 123.3, 126.6, 128.6, 131.5, 150.9. MS (EI): *m/z* = 221 [M^+ + Na^+]. Anal. Calcd for $C_{14}H_{14}O$: C, 84.81; H, 7.12. Found: C, 84.75; H, 7.15.