Efficient Synthesis of Dihydrobenzofurans via a Multicomponent Coupling of Salicylaldehydes, Amines, and Alkynes

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Received 7 April 2008

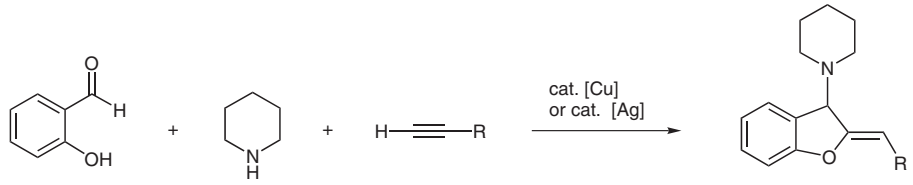
Abstract: A simple and efficient synthesis of dihydrobenzofurans was developed using a multicomponent coupling of various salicylaldehydes, amines, and alkynes. The use of aliphatic alkynes containing a heteroatom is critical to the success of the reaction.

Key words: multicomponent coupling, C–H bond reactions, tandem reactions, heterocycles, catalysis

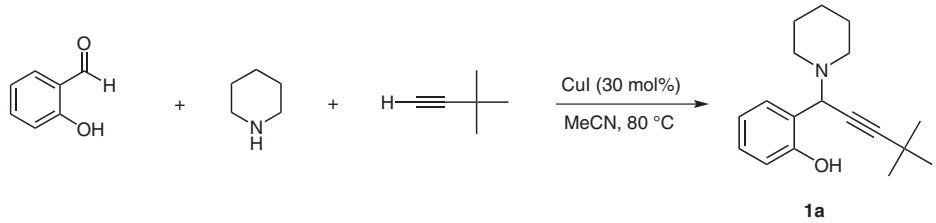
The dihydrobenzofuran core is an important subunit of many naturally occurring heterocycles, many of which are biologically active.[1] Therefore, chemists have developed many efficient methodologies for the synthesis of 2,3-dihydrobenzofurans derivatives, such as the radical cyclization,[2] the Bartoli reaction[3] or the dehydration method.[4] On the other hand, transition-metal-catalyzed cascade reactions have emerged as the method of choice to access heterocycles.[5] These cyclizations are often carried out under mild conditions with readily synthesized starting materials affording a wide variety of complex molecules. The key step to these syntheses is often the intramolecular Heck reaction.[6] Asymmetric variations of this reaction have also been reported.[7] Recently, we reported an annulation of phenol with dienes leading to dihydrobenzofurans.[8] To further our interest in such compounds, we wish to report another approach to dihydrobenzofurans via a three-component coupling using readily available components (Scheme 1).

We started our investigation using salicylaldehyde, piperidine, and 3,3-dimethylbut-1-yne in acetonitrile with 30 mol% CuI as catalyst (Scheme 2). However, only the aldehyde–amine–alkyne coupling (A^3-coupling) occurred and no cyclized product was obtained after stirring at 80 °C for 16 hours.[9]

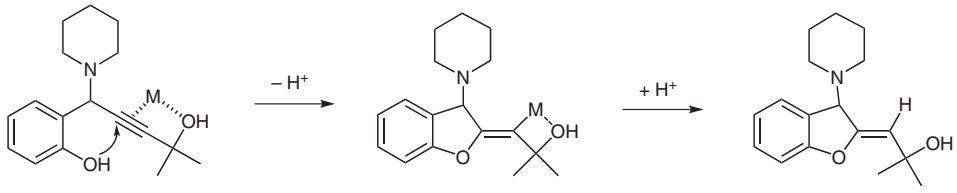
We then hypothesized that using a propargyl alcohol as the alkyne would help the cyclization. The Cu(I) species



Scheme 1 Multicomponent coupling of salicyldehyde, amine, and alkyne to generate dihydrobenzofurans

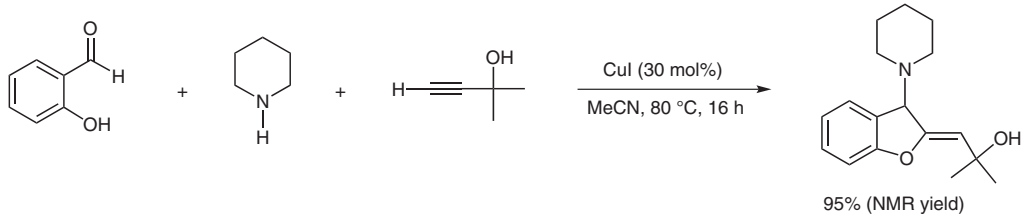


Scheme 2 Multicomponent coupling of salicylaldehyde, amine, and 3,3-dimethylbut-1-yne



Scheme 3 Proposed mechanism for the intramolecular cyclization

SYNLETT 2008, No. 12, pp 1897–1901
Advanced online publication: 02.07.2008
DOI: 10.1055/s-2008-1078573; Art ID: U03008ST



Scheme 4 Multicomponent coupling of salicylaldehyde, amine, and propargyl alcohol

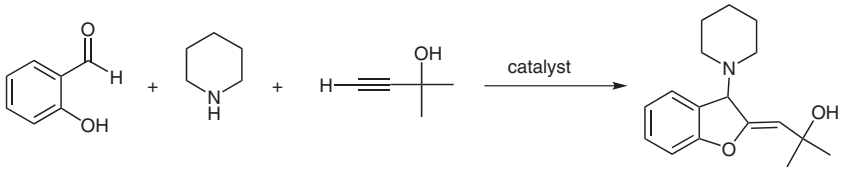
would coordinate to both the π-bond of the alkyne and the oxygen (Scheme 3).

Recently, Yamamoto et al. proposed a similar activation of alkynes in which a Cu(I) species coordinated to a carbonyl oxygen and a π-bond of the alkyne.[10] To much of our delight, the desired cyclized product was obtained exclusively with an excellent yield (Scheme 4). Although a similar reaction is known,[11] a stoichiometric amount of copper is required and the scope is limited.

Optimization of the reaction conditions was then carried out (Table 1). When AuI was used as a catalyst, only the A^3-addition product was obtained under the same reaction conditions (Table 1, entry 2).[12] Both AgCl and AgBr were are also effective for the cascade reaction (Table 1, entries 3 and 4).[13] Since CuI is much more economical than AgX and AuI, further investigations were carried out with CuI. Under microwave irradiation, we were able to shorten the reaction time, reduce the amount of catalyst, and eliminate the use of solvent (Table 1, entries 6 and 7).[14] We found that microwave irradiation at 130 °C for 30 minutes with 5 mol% CuI as catalyst in the absence of solvent provided optimal conditions in terms of yield and reaction time. Further attempts to shorten reaction time resulted in incomplete conversion (Table 1, entries 8 and 9).

Subsequently, various salicylaldehydes, amines, and propargyl alcohols were tested under our optimized reaction conditions (Table 2). We were pleased to find that the reaction was not limited to propargyl alcohols. Indeed, a protected propargyl amine can be used, as well as homopropargyl alcohols (Table 2, entries 3 and 4). The use of 1-hexynol also affords the cyclized product, albeit in a lower yield due to competing dimerization (Table 2, entry 5). Unfortunately, primary amines were not effective for this transformation. It should be noted that under the standard conditions (oil bath at 80 °C for 16 h), the reaction is equally effective with 5% CuI. On the other hand, the use of AgCl as a catalyst under our optimized microwave conditions led to low conversions. Hence, the reaction had to be run in an oil bath.

Table 1 Multicomponent Coupling of Salicylaldehyde, Piperidine and 2-Methyl-3-butyn-2-ol

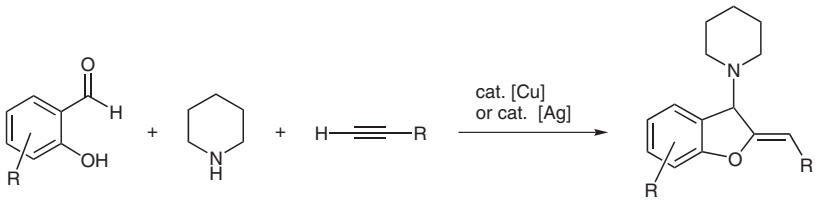


1a **2a** **3a** **4**

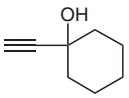
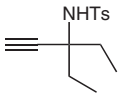
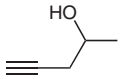
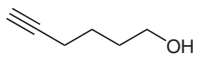
Entry[a]	Catalyst (mol%)	Conditions	Yield (%)[b]
1	CuI (30)	MeCN, 80 °C, 16 h	94
2	AuI (30)	MeCN, 80 °C, 16 h	0
3	AgBr (20)	MeCN, 80 °C, 16 h	88
4	AgCl (20)	MeCN, 80 °C, 16 h	94
5	CuI (30)	MW, 130 °C, 35 min, MeCN	74
6	CuI (30)	MW, 130 °C, 35 min, neat	80
7	CuI (5)	MW, 130 °C, 35 min, neat	90
8	CuI (5)	MW, 130 °C, 15 min, neat	54
9	CuI (5)	MW, 130 °C, 5 min, neat	28

[a] The reactions were performed with 1 equiv of **1a**, 2 equiv of **2a**, and equiv of **3a**.
[b] NMR yield using nitromethane as an internal standard.

Table 2 Copper- and Silver-Catalyzed Multicomponent Coupling of Salicylaldehyde, Amine, and Alkyne



1a: R = H
1b: R = naphthyl
1c: R = 5-Cl
1d: R = 3-OMe

Entry[a]	Aldehyde	Amine	Alkyne	Isolated yield (%)[c]
1	**1a**	**2a**	**3a**	85 (77)
2	**1a**	**2a**		81 (76)
3	**1a**	**2a**		53 (42)
4	**1a**	**2a**		88 (71)
5	**1a**	**2a**		58 (44)
6	**1a**		**3a**	44 (40)
7	**1a**		**3a**	88 (75)
8[b]	**1b**	**2a**	**3a**	80 (72)
9[b]	**1c**	**2a**	**3a**	71 (66)
10[b]	**1d**	**2a**	**3a**	82 (75)

[a] Reactions were run at 130 °C for 30 min in a microwave reactor using 1 equiv of aldehyde, 2 equiv of amine, and 2 equiv of alkyne under neat conditions with 5% CuI.
[b] Acetonitrile was used as a solvent.
[c] Value in parentheses correspond to reactions run in MeCN using 1 equiv of aldehyde, 2 equiv of amine, and 2 equiv of alkyne with 5% AgCl for 16 h in a oil bath at 80 °C.

The *Z*-isomer was obtained exclusively for all compounds (Figure 1).[15] This is consistent with a 5-*exo*-dig mechanism as proposed in Scheme 3. The metal coordinates to the π-bond of the alkyne and the oxygen. Intramolecular attack then occurs, followed by protonolysis to afford the product.

In conclusion, we have developed an expedient route to dihydrobenzofurans using copper- and silver-catalyzed multicomponent couplings under conventional heating as well as under microwave irradiations. The use of aliphatic alkynes bearing a heteroatom is crucial to the cyclization step. The scope, synthetic application, and mechanism of the method are under investigation in our laboratory.[16–18]

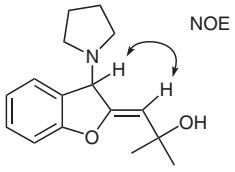


Figure 1 Determination of stereochemistry by NOE experiment

Acknowledgment

We are grateful to the Canada Research Chair (Tier I) foundation (to CJL), NSERC, and McGill University for support of this research.

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(16) **Typical Experimental Procedure for the Cu-Catalyzed Coupling of Aldehyde, Amine, and Alkyne under Microwave Irradiation**
In a 5 mL Biotage microwave vial, salicylaldehyde (209 μL, 2 mmol), morpholine (348 μL, 4 mmol), 2-methyl-3-butyn-2-ol (387 μL, 4 mmol), and CuI (19 mg, 0.10 mmol) were mixed. The vial was then capped and was subjected to microwave irradiation for 30 min at 130 °C. The crude mixture was directly isolated via column chromatography on SiO_2 (gradient eluent: hexane–EtOAc = 10:1 to 1:1) to give 241 mg (44% yield) of product (Table 2, entry 6).

(17) **Typical Experimental Procedure for the Ag-Catalyzed Coupling of Aldehyde, Amine, and Alkyne under Normal Heating Conditions**
Salicylaldehyde (209 μL, 2 mmol), morpholine (348 μL, 4 mmol), 2-methyl-3-butyn-2-ol (387 μL, 4 mmol), and AgCl (14.3 mg, 0.10 mmol) were mixed in a reaction flask at 80 °C in a oil bath in MeCN overnight. The solvent was removed under reduced pressure, and the crude mixture was isolated via column chromatography on SiO_2 (gradient eluent: hexane–EtOAc = 10:1 to 1:1) to give 220 mg (44% yield) of product (Table 2, entry 6).

(18) **2-Methyl-1-(3-piperidin-1-yl-3*H*-benzofuran-2-ylidene)propan-2-ol (Table 2, Entry 1)**
IR (neat): 3419 (br), 2933, 1696, 1463, 1158 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.36 (m, 1 H), 7.24 (m, 1 H), 6.99 (m, 1 H) 5.13 (s, 1 H), 4.79 (s, 1 H), 2.58 (m, 2 H), 2.40 (m, 2 H), 1.53–1.39 (m, 12 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.7, 152.2, 129.5, 126.3, 125.4, 122.2, 113.8, 109.9, 70.6, 67.8, 49.6, 30.9, 30.8, 26.5, 24.6 ppm. MS (EI): *m/z* (%) = 223 [M^+], 214, 189. HRMS: *m/z* calcd for $C_{17}H_{23}O_2N$: 273.1729; found: 273.17.
1-(3-Piperidin-1-yl-3*H*-benzofuran-2-ylidenemethyl)-cyclohexanol (Table 2, Entry 2)
IR (neat): 3419 (br), 2948, 1698, 1612, 1464, 1289 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.33 (m, 1 H), 7.17 (m, 1 H), 6.91 (m, 1 H), 6.85 (m, 1 H), 5.08 (s, 1 H), 4.74 (s, 1 H), 2.53 (m, 2 H), 2.32 (m, 2 H), 1.85–1.36 (m, 16 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.6, 152.9, 129.4, 126.2, 125.2, 122.1, 112.4, 109.9, 71.7, 67.8, 49.6, 30.0, 26.5, 25.8, 24.6, 23.0 ppm. MS (EI): *m/z* (%) = 313 [M^+], 229, 214. HRMS: *m/z* calcd for $C_{20}H_{27}O_2N$: 313.2036; found: 313.2042.
***N*-[1-Ethyl-1-(3-piperidin-1-yl-3*H*-benzofuran-2-ylidenemethyl)propyl]-4-methylbenzenesulfonamide (Table 2, Entry 3)**
IR (neat): 2970, 2802, 1696, 1612, 1594, 1461, 1157, 1094 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.64 (m, 2 H), 7.25 (m, 2 H), 6.92 (m, 2 H), 6.92 (m, 4 H), 5.26 (s, 1 H), 4.53 (s, 1 H), 4.19 (s, 1 H), 2.39 (m, 1 H), 2.27 (m, 1 H), 2.19 (s, 3 H), 2.03 (m, 3 H), 1.74 (m, 3 H), 1.34 (m, 6 H), 0.84 (m, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.5, 153.6, 142.5, 139.9, 129.6, 129.0, 127.4, 126.0, 125.3, 122.2, 110.0, 108.0, 67.8, 62.7, 49.6, 30.3, 26.3, 24.5, 21.6, 8.4 ppm. MS (EI): *m/z* (%) = 454 [M^+], 283, 214, 155. HRMS: *m/z* calcd for $C_{26}H_{34}O_3N_2S$: 454.2290; found: 454.2282.
4-(3-Piperidin-1-yl-3*H*-benzofuran-2-ylidene)butan-2-ol (Table 2, Entry 4)
IR (neat): 3382 (br), 2931, 1701, 1612, 1475, 1218, 1151 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.36 (m, 1 H), 7.20 (m, 1 H), 6.94 (m, 1 H), 6.80 (m, 1 H), 4.96 (m, 1 H), 4.78 (s, 1 H), 3.93 (sept, 1 H, *J* = 6.0 Hz), 2.39 (m, 6 H), 1.53–1.38 (m, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.1, 154.9, 129.5, 126.4, 125.9, 121.7, 109.8, 101.7, 68.1, 67.2, 49.6, 35.4, 26.4, 24.6, 23.1 ppm. MS (EI): *m/z* (%) = 273 [M^+], 214, 188. HRMS: *m/z* calcd for $C_{17}H_{23}O_2N$: 273.1729; found: 273.1723.
5-(3-Diethylamino-3*H*-benzofuran-2-ylidene)pentan-1-ol (Table 2, Entry 5)
IR (neat): 3412 (br), 2935, 1711, 1611, 1463, 1234 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.27 (m, 1 H), 7.11 (m, 1 H), 6.84 (m, 1 H), 6.74 (m, 1 H), 4.78 (t, 1 H, *J* = 6.4 Hz), 4.62 (s, 1 H), 3.46 (m, 2 H), 2.45–2.17 (m, 4 H), 1.56–1.26 (m, 12 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.2, 152.6, 129.4, 126.4, 125.7, 121.5, 109.5, 66.8, 61.9, 49.2, 35.3, 32.0, 29.8, 25.3, 20.1 ppm. MS (EI): *m/z* (%) = 287 [M^+], 214, 202. HRMS: *m/z* calcd for $C_{18}H_{25}O_2N$: 287.1872;

found: 287.1875.

2-Methyl-1-(3-morpholin-4-yl-3*H*-benzofuran-2-ylidene)propan-2-ol (Table 2, Entry 6)

IR (neat): 3419 (br), 2967, 1612, 1462, 1374, 1232, 1115 cm^{-1}. ^1H NMR (400 MHz; $CDCl_3$): δ = 7.41 (m, 1 H), 7.26 (m, 1 H), 7.01 (m, 1 H), 6.94 (m, 1 H), 5.15 (s, 1 H), 4.79 (s, 1 H), 3.66 (m, 4 H), 2.63 (m, 2 H), 2.41 (m, 2 H), 1.50 (s, 3 H), 1.48 (s, 3 H) ppm. ^{13}C NMR (75 MHz $CDCl_3$): δ = 157.7, 151.4, 136.1, 129.9, 126.3, 122.4, 114.5, 110.1, 70.6, 67.4, 48.6, 30.8, 30.8 ppm. MS (EI): *m/z* (%) = 275 [M^+], 216, 189, 131, 86. HRMS: *m/z* calcd for $C_{16}H_{21}O_3N$: 275.1521; found: 275.1519.

2-Methyl-1-(3-pyrrolidin-1-yl-3*H*-benzofuran-2-ylidene)propan-2-ol (Table 2, Entry 7)

IR (neat): 3430 (br), 2911, 1672, 1561, 1341, 1160 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.35 (m, 1 H), 7.19 (m, 1 H), 6.93 (m, 1 H), 6.87 (m, 1 H), 5.12 (s, 1 H), 4.74 (s, 1 H), 2.57 (m, 2 H), 2.36 (m, 2 H), 1.54–1.24 (m, 10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.6, 152.2, 129.5, 125.4, 122.2, 113.7, 109.9, 70.6, 67.8, 49.6, 30.9, 26.5, 24.6 ppm. MS (EI): *m/z* (%) = 258 [M^+], 189, 131. HRMS: *m/z* calcd for $C_{16}H_{21}O_2N$: 258.1494; found: 258.1491.

2-Methyl-1-{3-piperidin-1-yl-3*H*-naphtho[2,3-*b*]furan-2-ylidene}propan-2-ol (Table 2, Entry 8)

IR (neat): 3581 (br), 2934, 1688, 1522, 1249, 1161 cm^{-1}. ^1H NMR (400 MHz $CDCl_3$): δ = 8.18 (m, 1 H), 7.83 (m, 1 H), 7.75 (m, 1 H), 7.52 (m, 1 H), 7.38 (m, 1 H), 2.53 (m, 4 H), 1.64–1.32 (m, 12 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.2, 151.2, 131.2, 130.8, 130.5, 128.8, 127.9, 124.0, 124.0, 117.9, 115.1, 111.4, 70.9, 68.2, 49.3, 31.2, 31.1, 26.8, 25.0 ppm. MS (EI): *m/z* (%) = 323 [M^+], 264, 181. HRMS: *m/z* calcd for $C_{21}H_{25}O_2N$: 323.1885; found: 323.1879.

1-(5-Chloro-3-piperidin-1-yl-3*H*-benzofuran-2-ylidene)-2-methylpropan-2-ol (Table 2, Entry 9)

IR (neat): 3401 (br), 2936, 1702, 1608, 1469, 1234, 1154 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.34 (s, 1 H), 7.20 (m, 1 H), 6.86 (m, 1 H), 5.14 (m, 1 H), 4.76 (s, 1 H), 2.58 (m, 2 H), 2.39 (m, 2 H), 1.54–1.46 (m, 12 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.2, 152.1, 129.5, 127.4, 126.3, 114.2, 110.9, 70.6, 69.8, 67.8, 49.6, 30.9, 26.5, 24.5 ppm. MS (EI): *m/z* (%) = 307 [M^+], 248, 223. HRMS: *m/z* calcd for $C_{17}H_{22}O_2N^{35}Cl$: 307.1339; found: 307.1344. HRMS: *m/z* calcd for $C_{17}H_{22}O_2N^{37}Cl$: 309.1312; found: 309.1312.

1-(6-Methoxy-3-piperidin-1-yl-3*H*-benzofuran-2-ylidene)-2-methylpropan-2-ol (Table 2, Entry 10)

IR (neat): 3580 (br), 2938, 1736, 1699, 1620, 1444, 1280 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.22 (m, 1 H), 6.50 (m, 1 H), 5.09 (m, 1 H), 4.67 (s, 1 H), 3.75 (s, 3 H), 2.53 (m, 2 H), 2.31 (m, 2 H), 1.49–1.36 (m, 12 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.2, 158.9, 153.0, 126.5, 117.2, 113.8, 108.1, 96.1, 70.6, 67.4, 55.7, 49.4, 30.9, 30.8, 26.4, 24.6 ppm. MS (EI): *m/z* (%) = 303 [M^+], 244, 219. HRMS: *m/z* calcd for $C_{18}H_{25}O_3N$: 303.1834; found: 303.1831.

2-(4,4-Dimethyl-1-piperidin-1-yl-pent-2-ynyl)phenol (1b)

IR (neat): 2936, 2233, 1644, 1465, 1458, 1362, 1244, 1153 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.51 (m, 1 H), 7.22 (m, 1 H), 6.87 (m, 2 H), 4.88 (s, 1 H), 2.64 (m, 4 H), 1.68 (m, 6 H), 1.39 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.0, 129.3, 128.6, 122.1, 110.0, 116.4, 99.1, 95.41, 71.3, 60.7, 31.6, 28.0, 26.2, 24.4 ppm. MS (EI): *m/z* (%) = 271 [M^+], 186, 84. HRMS: *m/z* calcd for $C_{18}H_{25}ON$: 271.1936; found: 271.1933.