Tetrahedron Letters 56 (2015) 6629–6632

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

# Palladium(0)-catalyzed 5-*exo-dig O*-cyclization/coupling of ethyl 3-(2-alkynylphenyl)-3-oxopropanoates with aryl iodides to 1,3-dihydroisobenzofurans

Li-Lan Wei [b], Li-Mei Wei [b], Po-Yang Lin [c], Chin-Chau Chen [a], Wen-Bin Pan [b,*], Ming-Jung Wu [a,c,*]

[a] Department of Chemistry, National Sun Yat-sen University, Kaohsiung, Taiwan, ROC
[b] Department of Applied Chemistry and Materials Science, Fooyin University, Kaohsiung, Taiwan, ROC
[c] Department of Medicinal and Applied Chemistry, Kaohsiung Medical University, Kaohsiung, Taiwan, ROC

ARTICLE INFO

*Article history:*
Received 7 September 2015
Revised 8 October 2015
Accepted 10 October 2015
Available online 22 October 2015

*Keywords:*
1,3-Dihydroisobenzofurans
Palladium-catalyzed
5-*exo-dig*
*O*-Cyclization/coupling

ABSTRACT

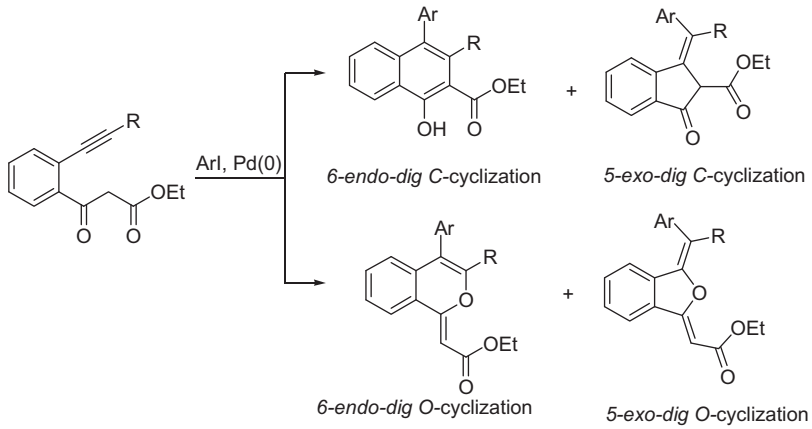
Palladium-catalyzed highly regioselective 5-*exo-dig O*-cyclization/coupling of a series of ethyl 3-(2-alkynylphenyl)-3-oxopropanoates with aryl iodides has been developed for the synthesis of (*Z*)-alkylidene-1,3-dihydroisobenzofuran derivatives. Reactions of ethyl 3-(2-alkynylphenyl)-3-oxopropanoates and aryl iodides are carried out in DMSO at 80 °C with 5 mol % $Pd(PPh_3)_4$ and 2 equiv of $Et_3N$ as a base for 4 h in modest yields.



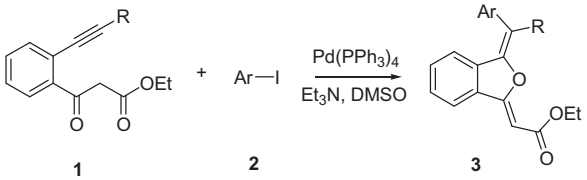
The dihydroisobenzofurans (phthalans), as useful building blocks[1] as well as key structural units in a broad range of natural products[2] and biologically important active compounds,[3] have attracted much attention in organic chemistry. As a result, much effort has focused on the synthesis of the functionalized phthalan derivatives. Over the years numerous routes available have been described to synthesize these compounds, with most of them requiring cyclization reactions of disubstituted alkynes through iodocyclization,[4] intramolecular Michael addition,[5] or intramolecular addition/cyclization involving the use of palladium,[6] and other metal- and metal-free catalyzed cyclization.[7] Therefore, the challenge remains to develop one-pot procedures for the production of highly functionalized alkylidene phthalans with high efficiency and regioselectivity. The palladium-catalyzed sequential intramolecular cyclization and coupling reactions of acetylenic molecules containing a heteronucleophile with organic halides or triflates are a well-established strategy that has led to the successful synthesis of a variety of heterocyclic compounds.[8] We have already disclosed several approaches to the palladium-catalyzed synthesis of heterocycles starting from acetylenic substrates.[9] In 2000, we have established a novel pathway to synthesize 3,4-disubstituted isoquinolines and diarylmethyleneisoindoles by the palladium-mediated coupling of 2-alkynylbenzonitriles with aryl iodides.[9a] In this Letter, the cyclization/coupling of 3-(2-alkynylphenyl)-3-keto esters with aryl iodides to give 1,3-dihydroisobenzofurans is particularly attractive because ethyl 2-alkynylbenzoyl acetates can be readily prepared from the corresponding ethyl 2-iodobenzoyl acetates with terminal alkynes. Cyclization reactions of this type, however, can be challenging because ethyl 3-(2-alkynylphenyl)-3-oxopropanoates can undergo both 6-*endo-dig* or 5-*exo-dig* cyclization modes which compete with each other, and the regioselectivity of these reactions must therefore be well-controlled to avoid the formation of intractable mixtures of five- and six-membered rings. In the case of the 5-*exo-dig* process, it is also necessary to control the nature of the addition to the triple bond (i.e., carbon- vs oxygen addition) to avoid the production of a mixture of isomeric phthalans and indanones (Scheme 1). Herein, we described a one-pot and regioselective synthesis of (*Z*)-alkylidenephthalan derivatives from 3-(2-alkynylphenyl)-3-oxopropanoates and aryl iodides through Pd(0)-promoted successive annulation/coupling reaction (Eq. 1).

* Corresponding authors.

http://dx.doi.org/10.1016/j.tetlet.2015.10.040
0040-4039/




**Scheme 1.**

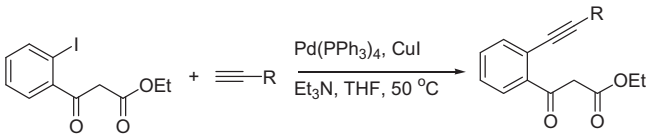



(1)

**1** **2** **3**

R=*n*-Am, *i*-Bu, *t*-Bu

The synthesis of starting material, ethyl 3-(2-hept-1-ynyl)phenyl)-3-oxopropanoate **1a**, from the palladium-catalyzed coupling reaction of ethyl 2-iodobenzoyl acetate with 1-heptyne was outlined in Eq. 2.



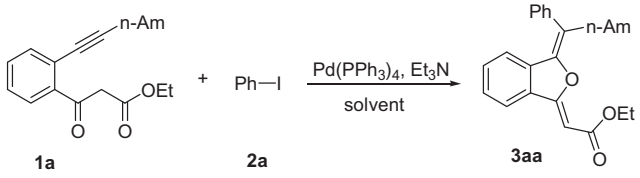

**1a**, R = $^{n}$Am (92%)
**1b**, R = $^{i}$Bu (94%)
**1c**, R = $^{t}$Bu (86%)

(2)

The initial attempt for the cyclization/coupled reaction of ethyl 3-(2-hept-1-ynyl)phenyl)-3-oxopropanoate **1a** and iodobenzene **2a** was carried out using 5 mol % $Pd(PPh_3)_4$ as the catalyst and 2 equiv of $Et_3N$ as a base at room temperature in DMSO for 24 h, and no desired product phthalan **3aa** was observed (Table 1, entry 1). However stirring the reaction mixture at 50 °C for 12 h, the expected product **3aa** was obtained in 50% yield (Table 1, entry 2). To optimize the reaction conditions, the cascade reactions were carried out with different solvents and at various temperatures. When the reaction of alkynyl ester **1a** with iodobenzene **2a** was conducted in THF at 50 °C for 12 h, the yield of product phthalan **3aa** was decreasing to 42% (Table 1, entry 3). Changing the reaction solvent from THF to DMF led to the 1,3-dihydroisobenzofuran product **3aa** in 45% yield (Table 1, entry 4). We demonstrated that polar aprotic solvent DMSO was most effective for the product formation. Upon heating the reaction mixture at 80 °C for 4 h, the yield of product **3aa** increased to 56% yield (Table 1, entry 5).[10] However upon increase of reaction temperature to 120 °C, the reaction started getting messy and the yield of **3aa** dropped to 27% (Table 1, entry 6).

With the optimized reaction conditions in hand, various aryl iodides bearing electron-donating or electron-withdrawing groups on the phenyl ring were reacted with ethyl 3-(2-hept-1-ynyl)phenyl)-3-oxopropanoate **1a** in the presence of 5 mol % $Pd(PPh_3)_4$ and 2 equiv $Et_3N$ at 80 °C in DMSO for 4 h to give the cyclization products **3aa**–**3ag** in modest yields. The results are summarized in Table 2. 4-Iodoanisole **2b** and 4-trifluoromethylphenyl iodide **2c** afforded the corresponding phthalans **3ab** and **3ac** in 55% and 58% yields, respectively, (Table 2, entries 2 and 3). 2-Iodothiophene **2d** gave **3ad** in 46% yield (Table 2, entry 4), which indicated that the electron rich aryl iodides gave the cyclization products in lower yields. 4-Iodobenzonitrile **2e** produced **3ae** in 53% yield (Table 2, entry 5). 4-Iodonitrobenzene **2f** was conducted with **1a** to produce **3af** in a higher yield (75%, Table 2, entry 6), indicating that 4-iodonitrobenzene **2f** with a strong electron-withdrawing group on the phenyl ring may accelerate the rate of the cyclization reaction. 4-Iodophenol **2g** only gave **3ag** in 20% yield (Table 2, entry 7). To further examine the generality of this cyclization/coupling reaction, other acetylenic β-keto esters **1b**–**c** bearing different alkyl substituents on the terminus alkyne are prepared from the appropriate ethyl *o*-iodobenzoyl acetate and corresponding terminal alkynes by the above palladium/copper-catalyzed coupling method (Eq. 2). More interestingly, the Sonogashira coupling reaction of ethyl 2-iodobenzoyl acetate with phenyl acetylene afforded

**Table 1**
Palladium-catalyzed sequential cyclization/coupling reaction under various conditions[a]

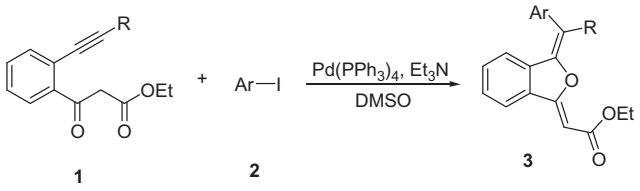



**1a** **2a** **3aa**

| Entry | Solvent | Temperature (°C) | Reaction time (h) | Product[b] (%) |
|---|---|---|---|---|
| 1 | DMSO | rt | 24 | NR[c] |
| 2 | DMSO | 50 | 12 | 50 |
| 3 | THF | 50 | 12 | 42 |
| 4 | DMF | 50 | 12 | 45 |
| 5 | DMSO | 80 | 4 | 56 |
| 6 | DMSO | 120 | 1 | 27 |

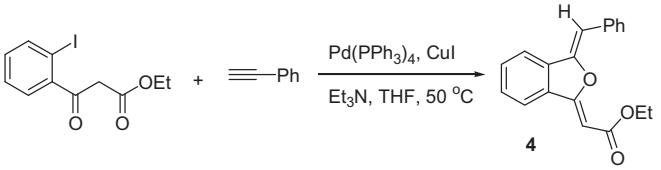
[a] All the reactions were carried out by using **1a** (0.17 mmol), **2a** (0.21 mmol), 5 mol % $Pd(PPh_3)_4$ (0.0085 mmol), 2 equiv $Et_3N$ (0.34 mmol), solvent (1 mL).
[b] Isolated yields.
[c] NR = no reaction.

**Table 2**
Palladium-catalyzed coupling reactions of ethyl 3-(2-alkynylphenyl)-3-oxopropanoates **1** with aryl iodides **2**




| Entry | R | Aryl iodides | Products (Yield %) |
|---|---|---|---|
| 1 | **1a** (R = $^{n}$Am) | **2a** (Ar = phenyl) | **3aa** (56) |
| 2 | **1a** | **2b** (Ar = 4-methoxyphenyl) | **3ab** (55) |
| 3 | **1a** | **2c** (Ar = 4-trifluoromethylphenyl) | **3ac** (58) |
| 4 | **1a** | **2d** (Ar = thiophen-2-yl) | **3ad** (46) |
| 5 | **1a** | **2e** (Ar = 4-cyanophenyl) | **3ae** (53) |
| 6 | **1a** | **2f** (Ar = 4-nitrophenyl) | **3af** (75) |
| 7 | **1a** | **2g** (Ar = 4-hydroxyphenyl) | **3ag** (20) |
| 8 | **1b** (R = $^{i}$Bu) | **2a** | **3ba** (38) |
| 9 | **1b** | **2b** | **3bb** (20) |
| 10 | **1b** | **2c** | **3bc** (31) |
| 11 | **1b** | **2d** | **3bd** (47) |
| 12 | **1c** (R = $^{t}$Bu) | **2a** | **3ca** (38) |
| 13 | **1c** | **2b** | **3cb** (27) |
| 14 | **1c** | **2c** | **3cc** (37) |
| 15 | **1c** | **2d** | **3cd** (35) |

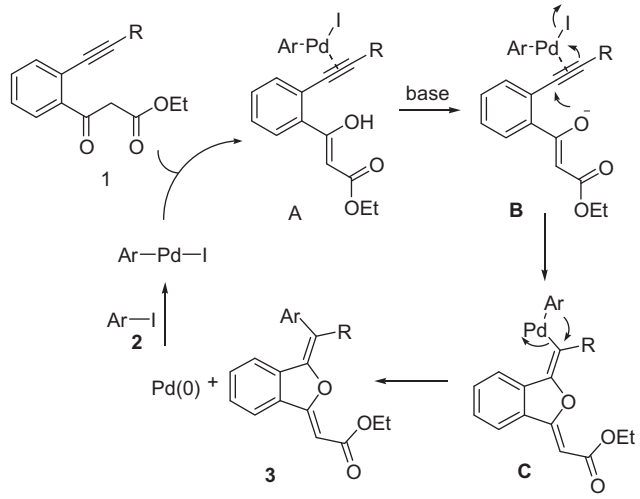
unexpected cyclization product, (*Z*)-ethyl 2-((*Z*)-3-benzylidene) isobenzofuran-1(3*H*)-ylidene)acetate **4**, in 82% yield (Eq. 3).[6d]




(3)

Treatment of ethyl 3-(2-(4-methylpent-1-ynyl)phenyl)-3-oxopropanoate **1b** with various aryl iodides **2a**–**2d** under the standard reaction conditions also gave the same coupling phthalan derivatives **3ba**–**3bd** in the 20–47% yields (Table 2, entries 8–11). Iodobenzene **2a** and 4-iodoanisole **2b** afforded the corresponding phthalans **3ba** and **3bb** in 38% and 20% yields, respectively, (Table 2, entries 8 and 9). Aryl iodides with an electron-withdrawing group such as 4-iodotrifluoromethylbenzene **2c** and 2-iodothiophene **2d** produced the cyclization products **3bc** and **3bd** in 31% and 47% yields, respectively, (Table 2, entries 10 and 11). Finally, the same reaction conditions apply to ethyl 3-(2-(3,3-dimethylbut-1-ynyl) phenyl)-3-oxopropanoate **1c** with various aryl iodides **2a**–**2d** gave the same cyclization products **3ca**–**3cd** in the 27–38% yields (Table 2, entries 12–15). Iodobenzene gave the cyclization product **3ca** in the yield of 38% (Table 2, entry 12). 4-Methoxyphenyl iodide produced the coupled product **3cb** in the 27% yield (Table 2, entry 13). Aryl iodides **2c** and **2d** yielded the cyclization products **3cc** and **3cd** in the yields of 37% and 35%, respectively, (Table 2, entries 14 and 15). According to the above results, substrates **1b**–**1c** with a bulky group such as isobutyl and *t*-butyl groups on the terminal alkynes may interfere the cyclization reaction and reduce the yield of the desired products. The chemical structure of the novel alkylidene-phthalan **3aa** was characterized by spectroscopic analysis.[11]

According to the above results and our previous work, we proposed a mechanism for this tandem process as shown in Scheme 2. This reaction pathway involves: (a) the oxidative addition of aryl iodide to Pd(0) to give an arylpalladium intermediate, (b) coordination of the carbon–carbon triple bond of **1** to σ-$C_{sp2}$-palladium complex to produce the $\eta^2$-palladium intermediate **A**, (c) deprotonation of the α-position of palladium complex **A** by $Et_3N$ to yield an palladium enolate ion **B**, followed by 5-*exo-trig* intramolecular nucleophilic *O*-attack of the enolate ion **B** to the activated carbon–carbon triple bond to give the vinylpalladium complex **C** and (d) reductive elimination of $Pd^0$ species from the palladium complex **C** to give the five-membered ring coupled product **3**. It is worthy to note that the tandem process proceeds in a steric- and regioselective manner.




**Scheme 2.**

In conclusion, we have demonstrated an efficient synthesis of the highly functionalized (*Z*)-alkylidene phthalans via palladium (0)-catalyzed sequential 5-*exo-trig* *O*-cyclization/coupling reactions of ethyl 3-(2-(substituted ethynyl)phenyl)-3-oxopropanoates with aryl iodides in DMSO. The stereochemistry was controlled by anti-addition of the electrophilic palladium and the nucleophilic oxygen to the alkyne. Currently, the synthetic application to pharmaceutical important phthalan derivatives is under investigation.

## Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.10.040.

## References and notes


1. (a) Meegalla, S. K.; Rodrigo, R. *J. Org. Chem.* **1991**, *56*, 1882; (b) Azzena, U.; Demartis, S.; Fiori, M. G.; Melloni, G.; Pisano, L. *Tetrahedron Lett.* **1995**, *36*, 8123; (c) Azzena, U.; Demartis, S.; Melloni, G. *J. Org. Chem.* **1996**, *61*, 4913; (d) Mikami, K.; Ohmura, H. *Org. Lett.* **2002**, *4*, 3355; (e) Siyang, H. X.; Wu, X. R.; Liu, H. L.; Wu, X. Y.; Liu, P. N. *J. Org. Chem.* **2014**, *79*, 1505.
2. (a) Strobel, G.; Ford, E.; Worapong, J.; Harper, J. K.; Arif, A. M.; Grant, D. M.; Fung, P. C. W.; Chau, R. M. W. *Phytochemistry* **2002**, *60*, 179; (b) Harper, J. K.; Arif, A. M.; Ford, E. J.; Strobel, G. A., Jr.; Porco, J. A.; Tomer, D. P.; Oneill, K. L.; Heider, E. M.; Grant, D. M. *Tetrahedron* **2003**, *59*, 2471; (c) Pahari, P.; Senapati, B.; Mal, D. *Tetrahedron Lett.* **2004**, *45*, 5109.
3. (a) Martin, C.; Mailliet, P.; Maddaluno, J. *J. Org. Chem.* **2001**, *66*, 3797; (b) Yang, H.; Hu, G. Y.; Chen, J.; Wang, Y.; Wang, Z. H. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5210.
4. Mancuso, R.; Mehta, S.; Gabriele, B.; Salerno, G.; Jenks, W. S.; Larock, R. C. *J. Org. Chem.* **2010**, *75*, 897.
5. (a) Mukhopadhyay, R.; Kundu, N. G. *Tetrahedron* **2001**, *57*, 9475; (b) Duan, S.; Cress, K.; Waynant, K.; Ramos-Miranda, E.; Herndon, J. W. *Tetrahedron* **2007**, *63*, 2959.
6. (a) Gabriele, B.; Salerno, G.; Fazio, A.; Pittelli, R. *Tetrahedron* **2003**, *59*, 6251; (b) Bacchi, A.; Costa, M.; Cà, N. D.; Fabbricatore, M.; Fazio, A.; Gabriele, B.; Nasi, C.; Salerno, G. *Eur. J. Org. Chem.* **2004**, 574; (c) Lemhadri, M.; Doucet, H.; Santelli, M. *Tetrahedron* **2005**, *61*, 9839; (d) Kobayashi, K.; Hashimoto, K.; Fukamachi, S.; Konishi, H. *Synthesis* **2008**, *7*, 1094; (e) Peng, P.; Tang, B.-X.; Pi, S.-F.; Liang, Y.; Li, J.-H. *J. Org. Chem.* **2009**, *74*, 3569; (f) Dell'Acqua, M.; Facoetti, D.; Abbiati, G.; Rossi, E. *Tetrahedron Lett.* **2011**, *67*, 1552; (g) Fan, Y. C.; Kwon, O. *Org. Lett.* **2012**, *14*, 3264; (h) Mancuso, R.; Ziccarelli, I.; Armentano, D.; Marino, N.; Salerno, G.; Gabriele, B. *J. Org. Chem.* **2014**, *79*, 3506.
7. (a) Chai, Z.; Xie, Z. F.; Liu, X.-Y.; Zhao, G.; Wang, J.-D. *J. Org. Chem.* **2008**, *73*, 2947; (b) Pawar, S. K.; Wang, C. D.; Bhunia, S.; Jadhav, A. M.; Liu, R. S. *Angew. Chem., Int. Ed.* **2013**, *52*, 7559; (c) Shen, Y. C.; Kwon, O. *Org. Lett.* **2014**, *16*, 5588; (d) Li, D. Y.; Shi, K. J.; Mao, X. F.; Chen, G. R.; Liu, P. N. *J. Org. Chem.* **2014**, *79*, 4602.
8. (a) Asao, N.; Nogami, T.; TaKahashi, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 764; (b) TsuKamoto, H.; Kondo, Y.; Ueno, T. *Org. Lett.* **2007**, *9*, 3033; (c) Liang, Z.; Ma, S.; Yu, J.; Xu, R. *J. Org. Chem.* **2007**, *72*, 9219; (d) Gabriele, B.; Mancuso, R.; Salerno, G. *J. Org. Chem.* **2008**, *73*, 7336.
9. (a) Wei, L. M.; Lin, C. F.; Wu, M. J. *Tetrahedron Lett.* **2000**, *41*, 1215; (b) Wu, M. J.; Lin, C. F.; Duh, T. H.; Lu, W. D.; Lee, J. L.; Lee, C. Y. *J. Chin. Chem. Soc.* **2004**, *51*, 183; (c) Wei, L. L.; Wei, L. M.; Pan, W. B.; Wu, M. J. *Synlett* **2004**, 1497.
10. *General procedure of the preparation of (Z)-alkylidene-1,3-dihydroisobenzofuran derivatives:* A slurry of the ethyl 3-(2-hept-1-ynyl)phenyl)-3-oxopropanoate **1a** (0.05 g, 0.17 mmol), iodobenzene **2a** (0.043 g, 0.21 mmol), 5 mol % $Pd(PPh_3)_4$ (0.01 g, 0.0085 mmol) and 2 equiv $Et_3N$ (0.34 mmol) in DMSO (1 mL) was stirred at 80 °C for 4 h. After cooling to room temperature, the reaction mixture was quenched with saturated aqueous $NH_4Cl$ solution and extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried over anhydrous $MgSO_4$. After filtration and removal of solvent, the residue was purified by column chromatography on silica gel using *n*-hexane–EtOAc (v/v, 50:1) as eluent to give the product **3aa** (56%).
11. *Compound* **3aa** *(56%) as a yellow liquid:* $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 7.55 (d, 1H, $J$ = 8.0 Hz), 7.45–7.38 (m, 3H), 7.32–7.23 (m, 3H), 7.13 (t, 1H, $J$ = 7.2 Hz), 6.42 (d, 1H, $J$ = 8.0 Hz), 5.55 (s, 1H), 4.30 (q, 2H, $J$ = 6.8 Hz), 2.86 (t, 2H, $J$ = 7.2 Hz), 1.46–1.22 (m, 6H), 0.85 (t, 6H, $J$ = 7.2 Hz); $^{13}C$ NMR ($CDCl_3$, 100 MHz): 166.1, 161.8, 148.1, 138.1, 133.8, 133.6, 131.0, 129.2, 129.2, 128.9, 128.9, 128.4, 127.8, 123.5, 122.6, 120.9, 88.5, 59.8, 33.4, 31.6, 27.1, 22.5, 14.5, 14.0; HMRS(EI); $m/z$ calcd for $C_{24}H_{26}O_3$: 362.1882; found: 362.1881.