# Studies on the Phthalidation of Heteroarenes: A Facile Preparation of 3-(Heteroaryl)phthalides via Triflic Acid Mediated Phthalidation

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**Abstract:** A triflic acid mediated heteroarylation of phthalaldehydic acid in 1,2-dichloroethane at reflux temperature leads to the formation of 3-heteroarylphthalides. This method for the phthalidation of heteroarenes can be utilized for the successful preparation of mono-, bis- and tris-heteroarylphthalides.

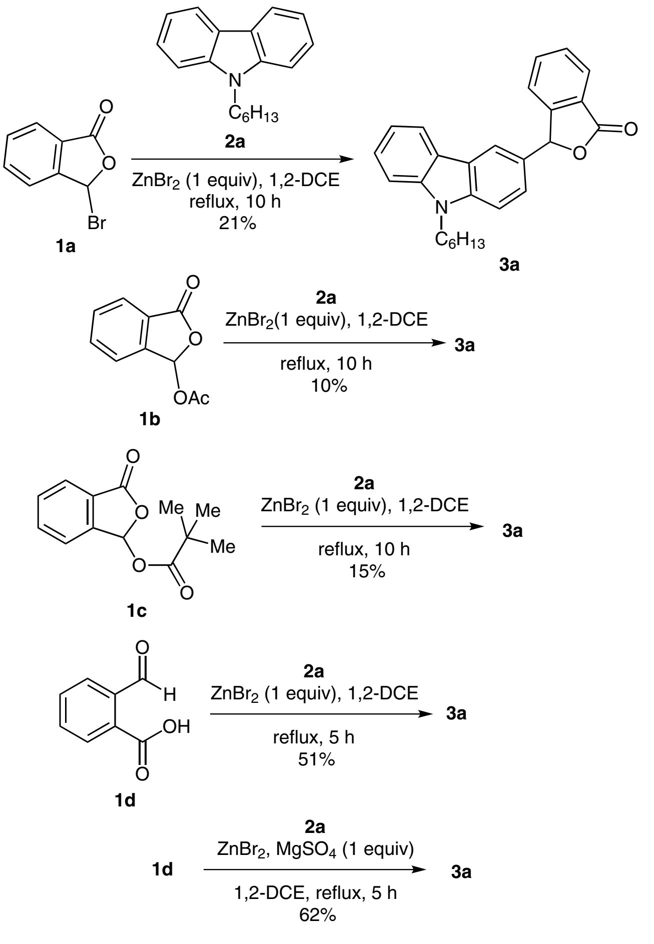
**Key words:** triflic acid, heteroarylation, 3-heteroarylphthalides, Brønsted acid, Lewis acid

3-Arylphthalides are routinely prepared by Friedel–Crafts phthaloylation of arenes followed by reductive cyclization, and we have adopted this method for the synthesis of a range of heteroarylphthalides.[1] Alternatively, halogen–metal exchange reactions of 2-halobenzoic acids,[2] as well as 2-halobenzoates[3] have been employed widely for the synthesis of 3-arylphthalides. The preparation of 3-arylphthalides has also been achieved by nickel-mediated coupling of 2-bromobenzoates with aryl aldehydes.[4] Other methods described for the formation of 3-arylphthalides involve transition metal mediated cascade reactions of phthalaldehydes with arylboronic acids.[5] A straightforward synthesis of several 3-arylphthalides has been achieved by the arylation of phthalaldehydic acid with arenes using aqueous sulfuric acid,[6] perchloric acid[7] and methanesulfonic acid.[8] The reaction of phthalaldehydic acid with aryl Grignards has also been employed for the synthesis of a wide variety of 3-arylphthalides.[9] Moreover, the preparation of 3-arylphthalides via palladium-mediated arylation of phthalaldehydic acid with an arylboronic acid has been disclosed.[10] An efficient synthesis of 3-indolyl substituted phthalides via Friedel–Crafts reactions of indoles with 2-formylbenzoic acid in aqueous medium has also been reported.[11]

The most common method for the preparation of 3-arylphthalides, involving Friedel–Crafts phthaloylation followed by reductive cyclization, suffers from the disadvantage of requiring excess Lewis acid as well as a reduction step. It should be noted that during the formation of the mono-ketoacid in the Friedel–Crafts step, the substrate is deactivated and hence the possibility for further phthaloylation is difficult. Moreover, in the case of electron-rich heteroarenes such as ethylenedioxythiophene (EDOT), the use of a Lewis acid led to polymerization.[12] Other reported methods are not amenable to the synthesis of complex heteroarylphthalides. The requirement for di- as well as tri-phthalide units on heteroarene scaffolds has prompted us to explore an alternative method to provide simultaneous incorporation of phthalide functions.

The Lewis acid mediated arylation of benzylic bromides has been exploited in our group for the synthesis of a variety of π-conjugated heterocycles.[13] In continuation of this work, we have undertaken a systematic study on the Lewis acid mediated arylation of 3-substituted phthalides **1a**–**c** and phthalaldehydic acid (**1d**).

The known bromo compound **1a**, upon heating at reflux temperature with 1-hexylcarbazole using one equivalent of zinc bromide ($ZnBr_2$) in 1,2-dichloroethane (DCE) for 10 hours led to the isolation of the desired lactone **3a** in



**Scheme 1** Carbazolylation of phthalides **1a**–**d** mediated by $ZnBr_2$

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**Table 1** Effect of the Catalyst on the Carbazolylation of **1d**

| Entry | Catalyst | Conditions[a] | Yield (%) |
|---|---|---|---|
| 1 | $ZnBr_2$ | reflux, 5 h | 62[c] |
| 2 | $BF_3 \cdot OEt_2$ | reflux, 4 h | 74[c] |
| 3 | $AlCl_3$ | r.t., 5 h | 21[c] |
| 4 | $ZrOCl_2 \cdot 8H_2O$ | reflux, 12 h | 46[c] |
| 5 | PTSA | reflux, 9 h | 51[c] |
| 6 | $CF_3SO_3H$[b] | reflux, 3 h | 80 |
| 7 | TMSOTf | r.t., 3 h | 40[c] |
| 8 | Amberlyst® | reflux, 12 h | 43[c] |
| 9 | Montmorillonite K10 | reflux, 4 h | 72[c] |

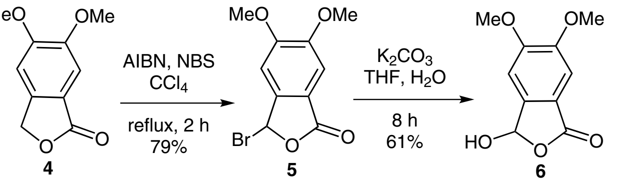
[a] Reactions were carried out using **2a** (1 equiv), **1d** (1.2 equiv), Brønsted/Lewis acid catalyst (1 equiv), anhydrous $MgSO_4$ (1 equiv).
[b] Triflic acid (0.2 equiv) was used.
[c] Calculated yield based on recovered **2a**.

21% yield. Similarly, the zinc bromide mediated carbazolylation of acetate **1b** and pivalate **1c** produced lactone **3a** in low yields. However, carbazolylation of phthalaldehydic acid (**1d**) using zinc bromide led to the formation of lactone **3a** in 51% yield (Scheme 1). The yield of the lactone **3a** could be enhanced further by performing the zinc bromide mediated carbazolylation in the presence of anhydrous magnesium sulfate. Thus, among substrates **1a**–**d**, the zinc bromide mediated carbazolylation was best with phthalaldehydic acid (**1d**). With substrates **1a**–**c**, the preferential coordination of zinc bromide with the lactone carbonyl unit would seem to be responsible for reducing significantly the yield of the phthalide **3a**.[14]

Accordingly, the carbazolylation of **1d** was carried out with different Lewis and Brønsted acid catalysts and the obtained results are presented in Table 1.

Among the Lewis acids employed for the carbazolylation of **1d**, boron trifluoride–diethyl ether complex ($BF_3 \cdot OEt_2$) gave the highest yield (Table 1, entry 2). The maximum yield of the lactone **3a** was obtained with triflic acid (Table 1, entry 6). It should be noted that, with the exception of triflic acid, in all the other cases, some unreacted **2a** was always recovered.

To generalize the phthalidation reaction, 5,6-dimethoxy-3-hydroxyphthalide (**6**) was prepared via benzylic bromination followed by hydrolysis (Scheme 2). $^1H$ NMR spectroscopic analysis of **6** confirmed its existence mainly as the hydroxyphthalide along with a minor amount of the corresponding phthalaldehydic acid.



**Scheme 2** Preparation of 5,6-dimethoxy-3-hydroxyphthalide (**6**)

The phthalidation of carbazole using triflic acid prompted us to explore the reaction with various heteroarenes (Table 2).

**Table 2** Phthalidation of Heteroarenes **2a**–**f**

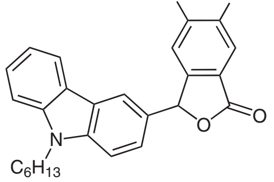
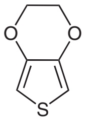
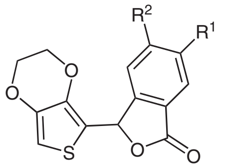
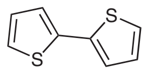
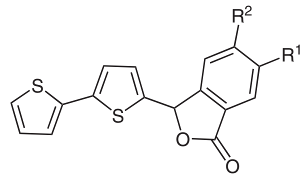
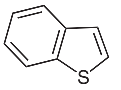
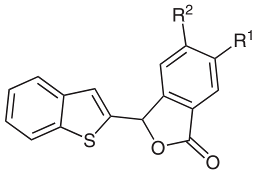
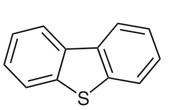
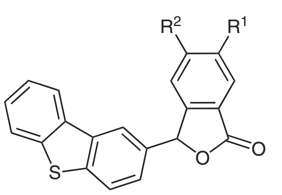
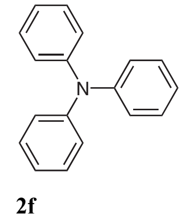
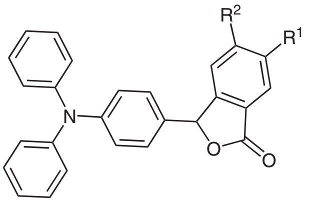
| Entry | Substrate | Product | Conditions[a] | Yield (%) |
|---|---|---|---|---|
| 1 | **2a** | <br>**3a** $R^1,R^2$ = H<br>**7a** $R^1,R^2$ = OMe | reflux, 3 h<br>reflux, 4 h | 80<br>70 |
| 2 | <br>**2b** | <br>**3b** $R^1,R^2$ = H<br>**7b** $R^1,R^2$ = OMe | r.t., 4 h<br>r.t., 4 h | 65<br>66 |

**Table 2** Phthalidation of Heteroarenes **2a**–**f** (continued)

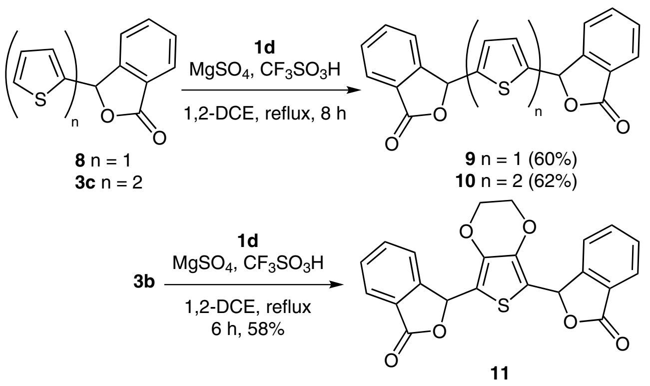
| Entry | Substrate | Product | Conditions[a] | Yield (%) |
|---|---|---|---|---|
| 3 | <br>**2c** | <br>**3c** $R^1,R^2 = H$<br>**7c** $R^1,R^2 = OMe$ | r.t., 5 h<br>r.t., 2 h | 73<br>68 |
| 4 | <br>**2d** | <br>**3d** $R^1,R^2 = H$<br>**7d** $R^1,R^2 = OMe$ | reflux, 5 h<br>reflux, 4 h | 80<br>78 |
| 5 | <br>**2e** | <br>**3e** $R^1,R^2 = H$<br>**7e** $R^1,R^2 = OMe$ | reflux, 7 h<br>reflux, 8 h | 70<br>69 |
| 6 | <br>**2f** | <br>**3f** $R^1,R^2 = H$<br>**7f** $R^1,R^2 = OMe$ | reflux, 6 h<br>reflux, 3 h | 76<br>75 |

[a] Reactions were carried out using substrate **2** (1 equiv), **1d** or **6** (1.2 equiv), triflic acid (0.2 equiv), anhydrous $MgSO_4$ (1 equiv), 1,2-DCE.

Carbazole **2a**, upon heating at reflux temperature with phthalaldehydic acid (**1d**) or 5,6-dimethoxy-3-hydroxyphthalide (**6**) using triflic acid (20 mol%) in 1,2-dichloroethane, furnished phthalides **3a** or **7a** in 80% and 70% yields, respectively (Table 2, entry 1). However, the expected phthalidation of highly electron-rich 3,4-ethylenedioxythiophene (**2b**) could be performed at room temperature affording the lactones **3b** and **7b** in very similar yields (Table 2, entry 2). In the case of 2,2′-bithiophene (**2c**), the phthalidation could also be performed at room temperature (Table 2, entry 3).

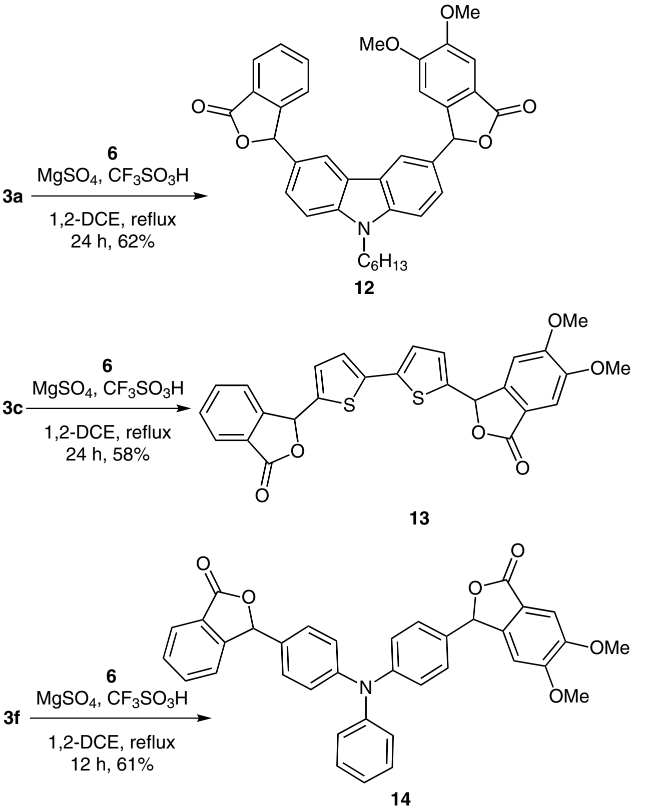
Benzo[*b*]thiophene (**2d**), upon heating at reflux temperature with **1d** or **6** using triflic acid in 1,2-dichloroethane led to the isolation of 2-benzo[*b*]thienylphthalides **3d** or **7d** in high yields (Table 2, entry 4). The phthalidation of dibenzothiophene (**2e**) could be smoothly performed with **1d** and **6** to afford the respective phthalides **3e** and **7e** (Table 2, entry 5). The reaction of triphenylamine (**2f**) with phthalaldehydic acid (**1d**) or 5,6-dimethoxy-3-hydroxyphthalide (**6**), using triflic acid in 1,2-dichloroethane at reflux temperature, furnished the respective lactones **3f** and **7f** in comparable yields. It should be noted that the presence of methoxy groups on the hydroxyphthalide **6** did not have any significant influence on the yields of the corresponding heteroarylphthalides. The obtained yields of 5,6-dimethoxyphthalides **7a**–**f** were comparable with those of phthalides **3a**–**f**.

The triflic acid mediated phthalidation reaction was then successfully applied to the synthesis of symmetrical bislactones. The thienyl lactones **8** and **3c**, upon reaction with phthalaldehydic acid (**1d**) using triflic acid (40 mol%) in 1,2-dichloroethane at reflux temperature, furnished the respective diphthalides **9** and **10**. Under similar conditions, 3,4-ethylenedioxythiophenyl lactone **3b** was converted into the bis-lactone **11** in 58% yield (Scheme 3).



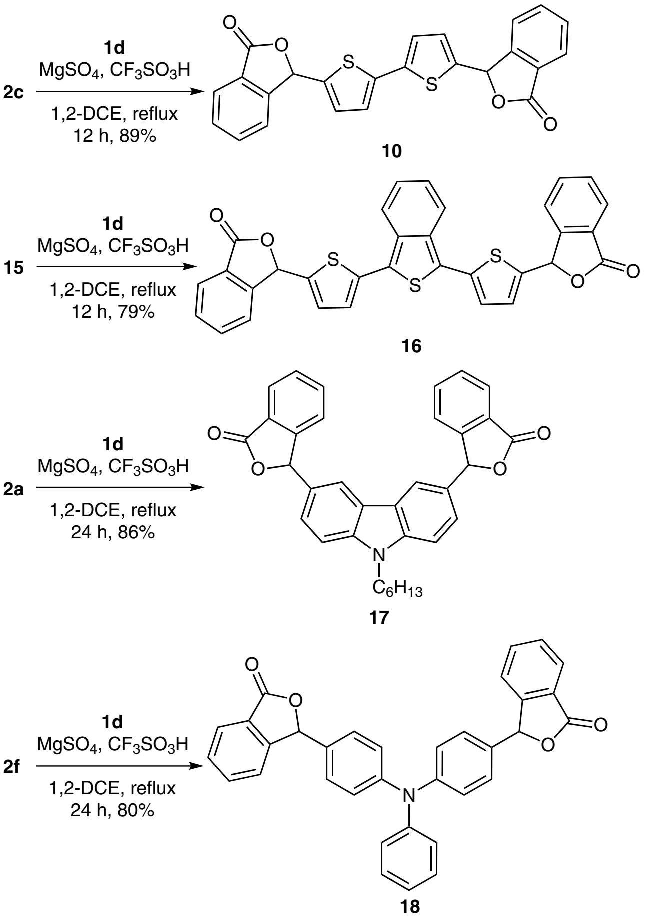
**Scheme 3** Preparation of symmetrical diphthalides

1-Hexylcarbazol-3-ylphthalide **3a**, upon reaction with 5,6-dimethoxy-3-hydroxyphthalide (**6**) in the presence of triflic acid in 1,2-dichloroethane at reflux temperature, led to the isolation of unsymmetrical diphthalide **12** in 62% yield (Scheme 4). Under identical conditions, the heteroarylphthalides **3c** and **3f** were converted into unsymmetrical diphthalides **13** and **14** in 58% and 61% yields, respectively.



**Scheme 4** Preparation of unsymmetrical diphthalides

Finally, one-pot bis-phthalidations of bithiophene **2c**, 1,3-dithienylbenzo[*c*]thiophene (**15**), *N*-hexylcarbazole (**2a**) and triphenylamine (**2f**) with phthalaldehydic acid (**1d**) (2.2 equiv) using triflic acid (40 mol%) in 1,2-dichloroethane at reflux temperature afforded the corresponding diphthalides **10**, **16**, **17** and **18** in good yields (Scheme 5).



**Scheme 5** One-pot bis-phthalidations of heteroarenes

Similarly, the reaction of triphenylamine (**2f**) with phthalaldehydic acid (**1d**) (3.3 equiv) led to the isolation of triphthalide **19** in 87% yield (Scheme 6). Under identical conditions, 1,3,5-tri(thiophen-2-yl)benzene (**20**) was smoothly converted into the respective triphthalide **21**.

In summary, a straightforward and general method for the preparation of 3-heteroarylphthalides has been achieved via triflic acid mediated Friedel–Crafts phthalidations of heteroarenes. This phthalidation reaction has been successfully applied to the synthesis of a variety of heteroaryl diphthalides and triphthalides. The heteroaryl diphthalides and triphthalides reported herein cannot be obtained via conventional Friedel–Crafts phthaloylation followed by reductive cyclization, thereby opening up the possibility to explore these readily available heteroarylphthalides as intermediates for the syntheses of benzo[*c*]thiophene analogues.[1,15,16] In particular, the heteroaryl diphthalides and triphthalides reported herein may find applications in the field of polycyclic aromatic heterocycles.[17]

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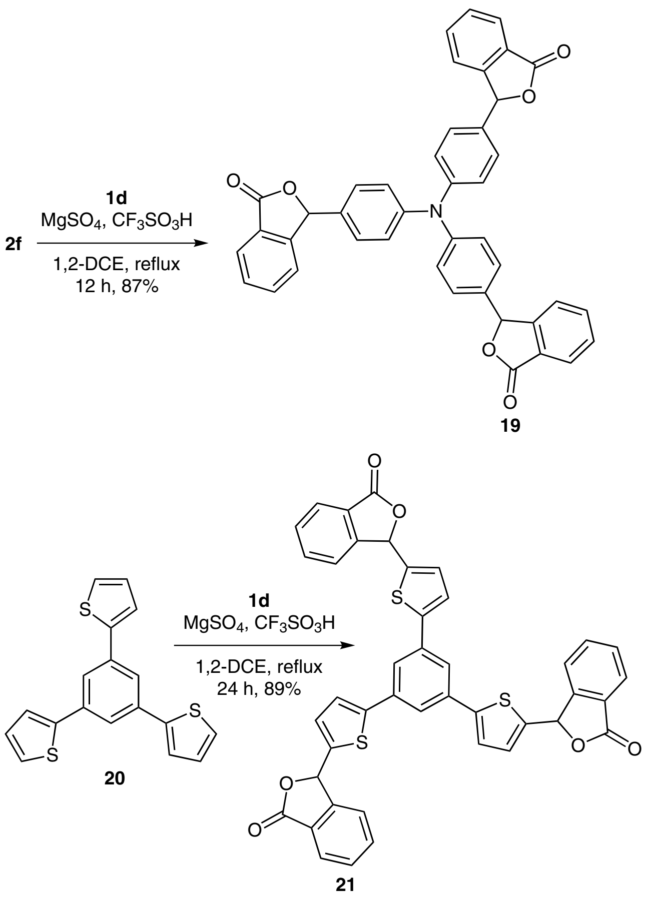
We thank the Department of Science and Technology (DST), New Delhi for financial support. M.N. and E.S. thank the Council of Scientific and Industrial Research (CSIR), New Delhi for JRF Fellow-



**Scheme 6** One-pot tri-phthalidations of heteroarenes

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**Supporting Information** for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(14) **General Procedure: Phthalidation of *N*-Hexylcarbazole (2a):** To a stirred suspension of *N*-hexylcarbazole **2a** (0.30 g, 1.20 mmol), 2-carboxybenzaldehyde (0.22 g, 1.43 mmol) and anhyd $MgSO_4$ (0.29 g, 1.20 mmol) in anhyd DCE (15 mL), 3 drops of triflic acid (0.04 g, 0.024 mmol) were added, and the mixture was refluxed for 3 h. It was then poured into sat. $NaHCO_3$ solution (50 mL), and the resulting mixture was extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic layers were washed with $H_2O$ (2 × 30 mL) and dried ($Na_2SO_4$). Removal of the solvent followed by column chromatographic purification (silica gel, 10% EtOAc in hexane) afforded lactone **3a** as a thick pale-yellow liquid (0.37 g, 80% yield). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 8.06–8.00 (m, 3 H, ArH), 7.64–7.55 (m, 2 H, ArH), 7.52–7.47 (m, 1 H, ArH), 7.42–7.32 (m, 3 H, ArH), 7.29–7.22 (m, 2 H, ArH), 6.58 (s, 1 H, CH), 4.24 (t, $J$ = 7.2 Hz, 2 H, $CH_2$), 1.87–1.78 (m, 2 H, $CH_2$), 1.34–1.27 (m, 6 H, $CH_2$), 0.90–0.86 (m, 3 H, $CH_3$). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 170.7, 150.2, 140.7, 134.1, 129.0, 126.2, 126.0, 125.8, 125.3, 124.7, 123.0, 122.8, 122.3, 120.3, 119.6, 119.0, 109.0, 108.8, 83.8, 43.0, 31.4, 28.7, 26.7, 22.4, 13.9.

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