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Synthesis of [5,6]-fused pyridocoumarins through aza-Claisen rearrangement of 6-propargylaminocoumarins

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ABSTRACT

[5,6]-Fused pyridocoumarins are prepared through aza-Claisen rearrangement and subsequent in situ cyclization of 6-propargylaminocoumarins under microwave irradiation in the presence of boron trifluoride diethyl etherate in *N*,*N*-dimethylformamide. During this process demethoxycarbonylation is observed in the corresponding 4-carbomethoxycoumarin derivatives.

Coumarin derivatives are an interesting class of heterocyclic system since the coumarin ring is an essential core moiety in a variety of natural and synthetic biologically active compounds.[1–7] In particular fused coumarins, among them pyridocoumarins, have been reported to possess antiallergic,[8] antidiabetic,[9] analgesic,[10,11] antiinflammatory,[11] and antimicrobial[11] properties.

The synthesis of pyridocoumarins has been achieved either by formation of the pyridine[7,9–22] or the pyranone[7,23–29] moieties. Construction of the pyridine moiety involves iodocyclization of 6-(but-2-ynyl)aminocoumarin in the presence of I_2, a process developed by Majumdar et al.,[12] the Pd-catalyzed Heck cyclization[13–15] of (2′-bromo)benzylaminocoumarins to dihydropyrido[3,2-*g*]- or [2,3-*c*]coumarins, the Skraup reaction[16] on 6-nitrocoumarin, the reactions of aminocoumarins with glycerol,[17] malondialdehyde,[18] ethyl benzoylacetate,[19] alkyl vinyl ketones[10] or under Vilsmeier conditions,[20] the Diels–Alder reactions of the *O*-methyl imine of 2-oxo-2*H*-chromene-4-carboxaldehyde with dienophiles[21] and reactions of 4-oxo-4*H*-chromene-3-carbaldehyde with enamines.[9,22] The formation of the pyranone moiety is realized from quinolinols by Pechmann condensation[23,24] or reactions[25] with DMAD and PPh_3, from quinolinequinones via Wittig reactions[25] or condensation with diethyl aminofumarate,[26] by the oxidation of a pyran ring formed in situ by electrocyclization of *cis*-dienals[27] and demethylation and condensation of *o*-substituted (2′-methoxyphenyl)pyridine carboxylic acids.[28,29]

Pyridine derivatives have also been prepared by electrophilic cyclization of propargylamines in the presence of gold,[30] copper[30,31] or mercury[32] salts. Propargylamines, on aza-Claisen rearrangement[33–35] resulted in pyrrole[36–38] or dihydropyridine[39,40] derivatives. Decomposition[31] occurred during acid-catalyzed rearrangement of propargylamines at 100 °C. $BF_3{\cdot}Et_2O$ has been used for the aza-Claisen rearrangement of *N*-allylanilines to *o*-allylanilines under heating[41,42] or microwave irradiation in xylenes.[43] Recently,[44] we reported on the Claisen rearrangements of reactions of propargyloxycoumarins under microwave irradiation, which in the presence of $BF_3{\cdot}Et_2O$ in DMF resulted in pyranocoumarins, while with *N*-methylformamide (NMF) gave furocoumarins. In the course of our investigations on the synthesis[21,25] of fused pyridocoumarin derivatives in order to study further their biological activities, we report here on the application of $BF_3{\cdot}Et_2O$ in the synthesis of the title compounds from 6-propargylaminocoumarins. The reactions studied and the products obtained are depicted in Schemes 1–3.

Propargylation of 6-aminocoumarin (**1a**)[45] with propargyl bromide (**2**) in dry acetone in the presence of K_2CO_3 under reflux for 5 days gave 6-propargylaminocoumarin (**3a**) (54%) and 6-(dipropargylamino)coumarin (**4a**) (8%), while 33% of the starting material remained unreacted (Scheme 1). Microwave irradiation of a solution of compound **3a** in $BF_3{\cdot}Et_2O$ and DMF at 200 °C for 9 h (the mixture was monitored by TLC every hour) resulted in the 3*H*-pyrano[3,2-*f*]quinolin-3-one (**5a**)[16,27] (38%), while 49% of the starting material remained unchanged. Analogous propargylation of 6-amino-7-methylcoumarin (**1b**)[46] led to 7-methyl-6-propargylaminocoumarin (**3b**) (56%) (38% of the starting amine

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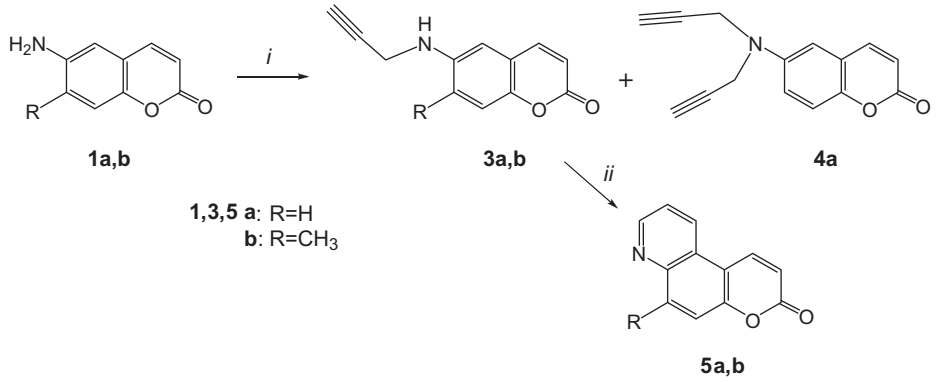
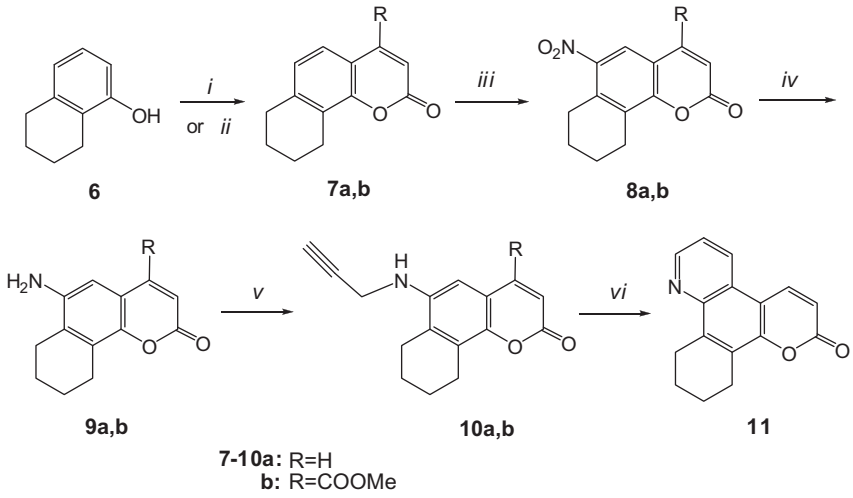
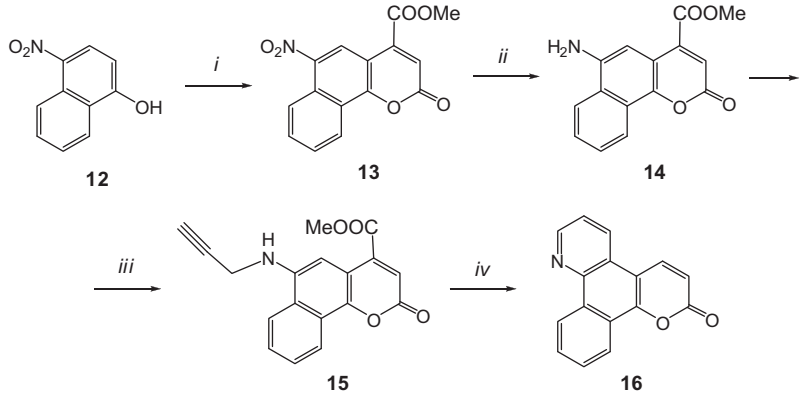


Scheme 1. Reagents and conditions: (i) Propargyl bromide (**2**), K_2CO_3, acetone (dry), reflux, 5 d; (ii) $BF_3{\cdot}Et_2O$, DMF, MW, 200 °C, 9 h.



Scheme 2. Reagents and conditions: (i) Ethyl propynoate, TFA, $Pd(OAc)_2$ (1.25 mol %), 0 °C (5 min) then rt (24 h) (for **7a**); (ii) Ph_3P, DMAD, CH_2Cl_2, 0 °C (10 min) then reflux (48 h) (for **7b**); (iii) concd H_2SO_4 (cooling, stirring 30 min), KNO_3, rt 24 h; (iv) HCOOH, Et_3N, 10% Pd/C, 100 °C, 20 min; (v) propargyl bromide (**2**), K_2CO_3, acetone (dry), reflux, 5 d; (vi) $BF_3{\cdot}Et_2O$, DMF, MW, 200 °C, 2.5 h.

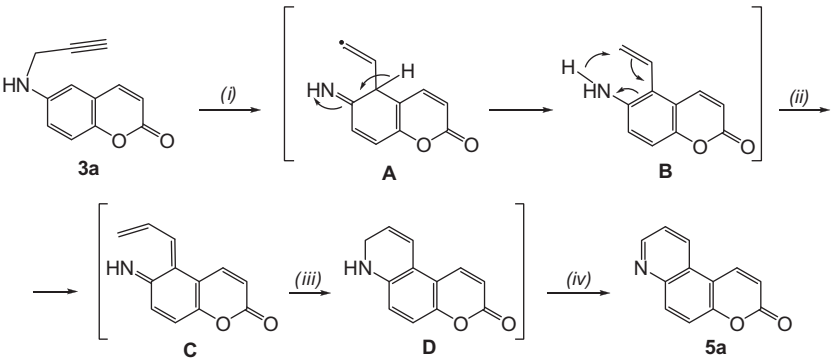


Scheme 3. Reagents and conditions: (i) Ph_3P, DMAD, toluene, 0 °C (10 min) then reflux (3 d); (ii) HCOOH, Et_3N, 10% Pd/C, 100 °C, 20 min; (iii) propargyl bromide (**2**), K_2CO_3, DMF (dry), 70 °C, 48 h; (iv) $BF_3{\cdot}Et_2O$, DMF, MW, 200 °C, 3 h.

remained unreacted), which on microwave irradiation gave the pyridocoumarin **5b**[47] in 50% yield (22% of **3b** remained unreacted).

The fused coumarin **7a** was isolated[47] in 80% yield from the reaction[48] of a solution of 5,6,7,8-tetrahydro-1-naphthol (**6**) in TFA with ethyl propynoate in the presence of a catalytic amount of $Pd(OAc)_2$. Nitration[46] of coumarin **7a** with KNO_3 in H_2SO_4 resulted in nitrocoumarin **8a** (78%). In the NOE experiments on compound **8a** there was a 2% interaction between H-4 and H-5 which helped to confirm the structure.

Reduction[46] of the nitro compound **8a** with HCOOH/Et_3N in the presence of 10% Pd/C at 100 °C gave the amine **9a** (77%) (Scheme 2). Treatment of **9a** in refluxing acetone for 5 days with propargyl bromide (**2**) and K_2CO_3 led to propargylamino derivative **10a** (59%). The fused pyridocoumarin **11** (60%) was obtained by microwave



Scheme 4. (i) [3,3] Rearrangement; (ii) [1,5-*H*] sigmatropic shift; (iii) 6n-electrocyclization; (iv) oxidation.

irradiation of a solution of **10a** in DMF in the presence of $BF_3{\cdot}Et_2O$ at 200 °C for 2.5 h.

4-Carbomethoxycoumarin **7b** (71%) was prepared from the reaction[25] of naphthol **6** with dimethylacetylenedicarboxylate (DMAD) in the presence of PPh_3. Nitration of compound **7b** in analogy to **7a** resulted in nitrocoumarin **8b** (79%), which was reduced to amine **9b** (78%). Propargylation of the latter led to the propargylaminocoumarin derivative **10b** (63%), which on microwave irradiation at 200 °C with $BF_3{\cdot}Et_2O$ in DMF for 2.5 h gave again the pyridocoumarin **11** (52%) after demethoxycarbonylation of the intermediate ester. This ester hydrolysis and subsequent decarboxylation possibly occurred after formation of the pyridine ring. This is similar to demethoxycarbonylation of methyl carboxylates in quinoline in the presence of Cu at 170–175 °C.[49]

The 6-nitrocoumarin derivative **13** was synthesized from the reaction[25] of 4-nitro-1-naphthol (**12**) with DMAD and PPh_3 in toluene in 85% yield. Reduction[46] of nitro compound **13** as before gave the amine **14** (85%). The propargylaminocoumarin **15** was obtained in 53% yield from the reaction of amine **14** with propargyl bromide (**2**) in the presence of K_2CO_3 by heating in DMF at 70 °C for 48 h (36% of **14** was recovered). Treatment of derivative **15** with $BF_3{\cdot}Et_2O$ in DMF at 200 °C for 3 h under microwave irradiation gave 2*H*-benzo[*h*]pyrano[3,2-*f*]quinolin-2-one (**16**) (42%), again demethoxycarbonylation occured.

A mechanistic proposal involving aza-Claisen rearrangement for the transformation of propargylaminocoumarins into fused pyridocoumarins in analogy to the Claisen rearrangement of propargyloxycoumarins[44] is shown in Scheme 4. Initial [3,3]-rearrangement of propargylaminocoumarin **3a** gave allenyl intermediate **A**, which undergoes aromatization to the *o*-aminoallenyl derivative **B**. A [1,5-*H*]-shift in **B** led to **C**, which cyclized to the dihydropyridine derivative **D**. Oxidation of the latter under the reaction conditions afforded pyridocoumarin **5a**.

In conclusion, we have demonstrated the use of boron trifluoride diethyl etherate under microwave irradiation conditions for the formation of pyridocoumarin derivatives in moderate to good yields.

Acknowledgments

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47. Procedures and selected data:
(a) *Synthesis of 7,8,9,10-tetrahydro-2H-benzo[h]chromen-2-one (**7a**).* To an ice-cold solution of compound **6** (0.296 g, 2 mmol) in TFA (2 ml) were added $Pd(OAc)_2$ (6 mg, 0.025 mmol) and ethyl propynoate (0.39 g, 0.41 ml, 4 mmol). The mixture was stirred for 5 min under cooling, stirred for 22 h at room

temperature and neutralized with 10% $NaHCO_3$ solution. Extraction with CH_2Cl_2 (2 × 50 ml), drying of the organic layer ($MgSO_4$), evaporation of the solvent and separation by column chromatography [silica gel, hexane/EtOAc (5:1)] gave, after elution of unreacted starting material (5%), compound **7a** (80% yield), light-green crystals, mp 105–106 °C (CH_2Cl_2), IR (KBr): 1712, 1604 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.75–1.94 (m, 4H), 2.98 (t, 2H, J = 5.5 Hz), 3.04 (t, 2H, J = 5.5 Hz), 6.35 (d, 1H, J = 9.5 Hz), 7.01 (d, 1H, J = 7.7 Hz), 7.21 (d, 1H, J = 7.7 Hz), 7.66 (d, 1H, J = 9.5 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.0, 22.4, 22.5, 29.9, 114.9, 124.3, 125.2, 125.5, 142.5, 143.9, 152.2, 155.0, 161.2; MS (ESI): 201 $[M+H]^+$, 223 $[M+Na]^+$; Anal. Calcd for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 77.72; H, 6.23.

(b) *Synthesis of 6-nitro-7,8,9,10-tetrahydro-2H-benzo[h]chromen-2-one (**8a**).* Coumarin **7a** (0.3 g, 1.5 mmol) was added under stirring over 30 min to ice-cold concentrated H_2SO_4 (2 ml). KNO_3 (0.192 g, 1.91 mmol) was then added and the mixture stirred for 24 h and neutralized with an ice-cold 10% $NaHCO_3$ solution. The precipitated solid was filtered to give compound **8a** (78%), brown crystals, mp 138–140 °C (EtOAc), IR (KBr): 1743, 1613 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.86–1.89 (m, 4H), 2.98 (t, 2H, J = 6.5 Hz), 3.07 (t, 2H, J = 6.5 Hz), 6.50 (d, 1H, J = 9.6 Hz), 7.71 (d, 1H, J = 9.6 Hz), 7.95 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.8, 21.7, 23.2, 27.1, 115.6, 117.5, 121.4, 128.6, 136.9, 142.5, 145.9, 153.9, 159.5; MS (ESI): 268 $[M+Na]^+$; Anal. Calcd for $C_{13}H_{11}NO_4$: C, 63.67; H, 4.52; N, 5.71. Found: C, 63.54; H, 4.56; N, 5.73.

(c) *Synthesis of 6-amino-7,8,9,10-tetrahydro-2H-benzo[h]chromen-2-one (**9a**).* Nitrocoumarin **8a** (0.245 g, 1 mmol) was added under stirring to a mixture of Et_3N (8 ml), HCOOH (1 ml) and 10% Pd/C (28 mg, 0.45 mmol). The resulting mixture was then heated at 100 °C for 20 min, poured onto ice (10 g) and extracted with CH_2Cl_2 (7 × 30 ml). The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated to give aminocoumarin **9a** (77%), red crystals, mp 155–157 °C (CH_2Cl_2), IR (KBr): 3453, 3347, 1705, 1646 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.76–1.94 (m, 4H), 2.53 (t, 2H, J = 5.2 Hz), 2.89 (t, 2H, J = 5.2 Hz), 5.01 (br s, 2H), 6.33 (d, 1H, J = 9.5 Hz), 6.59 (s, 1H) 7.57 (d, 1H, J = 9.5 Hz), ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.3, 22.6, 25.1, 28.9, 109.4, 114.7, 119.1, 120.3, 135.4, 141.4, 150.2, 151.9, 160.4; MS (ESI): 216 $[M+H]^+$; 238 $[M+Na]^+$; Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.57; H, 6.09; N, 6.51. Found: C, 72.48; H, 6.14; N, 6.57.

(d) *General procedure for the propargylation of 6-aminocoumarins.* Propargyl bromide (**2**) (96 mg, 0.06 ml, 0.7 mmol) and anhydrous K_2CO_3 (74 mg, 0.7 mmol) were added to a solution of 6-aminocoumarin **9a** (0.15 g, 0.7 mmol) in dry acetone (15 ml) and refluxed for 5 d. The resulting mixture was filtered, while hot and rinsed with acetone. The filtrate was evaporated and subjected to column chromatography [silica gel, hexane/EtOAc (5:1)] to give, from the faster moving band [before unreacted starting amine (25%)], *6-(prop-2-yn-1-ylamino)-7,8,9,10-tetrahydro-2H-benzo[h]chromen-2-one (**10a**)* (59% yield), white crystals, mp 92–93 °C (CH_2Cl_2), IR (KBr): 3379, 2125, 1705 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.73–1.94 (m, 4H), 2.26 (t, 1H, J = 2.0 Hz), 2.50 (t, 2H, J = 5.7 Hz), 2.92 (t, 2H, J = 5.7 Hz), 3.83 (br s, 1H), 4.01 (d, 2H, J = 2.0 Hz), 6.36 (d, 1H, J = 9.6 Hz), 6.56 (s, 1H), 7.67 (d, 1H, J = 9.6 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.7, 22.6, 33.8, 34.3, 41.1, 69.1, 83.2, 108.3, 117.2, 122.7, 125.9, 131.6, 137.4, 140.2, 144.9, 161.6; MS (ESI): 254 $[M+H]^+$, 276 $[M+Na]^+$; Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.99; H, 5.85; N, 5.61.

(e) *General procedure for the synthesis of pyridocoumarins from 6-propargylaminocoumarins.* To a solution of compound **10a** (30 mg, 0.12 mmol) in DMF (1 ml), $BF_3{\cdot}Et_2O$ (0.03 ml, 0.24 mmol) was added and the mixture irradiated using a Biotage (Initiator 2.0) scientific microwave oven at 200 °C for 2.5 h (the mixture was monitored by TLC every 30 min). After cooling, the mixture was poured into H_2O (30 ml) and extracted with Et_2O (3 × 20 ml). The ether layer was dried ($MgSO_4$), concentrated and separated by column chromatography [silica gel, hexane/EtOAc (3:1)] to give unreacted starting material (23%) followed by *9,10,11,12-tetrahydro-2H-benzo[h]pyrano[3,2-f]quinolin-2-one **11*** (60% yield), white crystals, mp 93–94 °C (CH_2Cl_2), IR (KBr): 1702, 1645, 1612 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.79–1.96 (m, 4H), 2.98–3.08 (m, 2H), 3.38–3.47 (m, 2H), 6.57 (d, 1H, J = 9.8 Hz), 7.56 (dd, 1H, J_1 = 4.2 Hz, J_2 = 8.4 Hz), 8.41 (d, 1H, J = 9.8 Hz), 8.50 (d, 1H, J = 8.4 Hz), 8.97 (d, 1H, J = 4.2 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.1, 22.3, 25.6, 29.8, 114.8, 121.9, 123.5, 128.6, 129.7, 138.7, 142.1, 146.2, 148.6, 152.6, 154.8, 159.5; MS (ESI): 252 $[M+H]^+$, 274 $[M+Na]^+$; Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.77. Found: C, 76.46; H, 5.27; N, 5.73.

(f) *6-Methyl-3H-pyrano[3,2-f]quinoline-3-one (**5b**).* Yield 50%, white crystals, mp 198–200 °C (lit.[50] mp 200 °C); ^1H NMR (300 MHz, $CDCl_3$) δ 2.07 (s, 3H), 6.56 (d, 1H, J = 9.8 Hz), 7.58 (s, 1H), 7.61 (dd, 1H, J_1 = 4.2 Hz, J_2 = 8.5 Hz), 8.40 (d, 1H, J = 9.8 Hz), 8.55 (dd, 1H, J_1 = 1.6 Hz, J_2 = 8.5 Hz), 9.01 (dd, 1H, J_1 = 1.6 Hz, J_2=4.2 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.8, 111.2, 115.3, 120.4, 122.4, 124.1, 129.8, 138.2, 144.0, 145.0, 148.9, 153.6, 160.7.

(g) *2H-Benzo[h]pyrano[3,2-f]quinoline-2-one (**16**).* Yield 42%, light-yellow crystals, mp 238–241 °C (lit.[50] mp 243 °C); ^1H NMR (300 MHz, $CDCl_3$) δ 6.65 (d, 1H, J = 9.8 Hz), 7.63 (dd, 1H, J_1 = 4.4 Hz, J_2 = 8.3 Hz), 7.80–7.92 (m, 2H), 8.42 (d, 1H, J = 9.8 Hz), 8.51 (dd, 1H, J_1 = 1.6 Hz, J_2 = 8.3 Hz), 8.64 (dd, 1H, J_1 = 1.7 Hz, J_2 = 7.5 Hz), 9.02 (dd, 1H, J_1 = 1.6 Hz, J_2 = 4.4 Hz), 9.33 (dd, 1H, J_1 = 1.6 Hz, J_2 = 7.5 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 116.2, 120.0, 122.8, 123.4, 125.1, 129.4, 129.7, 130.2, 133.4, 139.1, 140.8, 142.4, 148.7, 148.9, 154.0, 161.9.

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