Copper-Mediated N-Arylations of Hydantoin

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ABSTRACT: A set of two broadly applicable procedures for the N-arylation of hydantoin is reported. The first one relies on the use of stoichiometric copper(I) oxide under ligand- and base-free conditions and enables a clean regioselective arylation at the N3 nitrogen atom, while the second one is based on the use of catalytic copper(I) iodide and trans-NN'-dimethylcyclohexane-1,2-diamine and promotes arylation at the N3 nitrogen atom. Importantly, the combination of these two procedures affords a straightforward entry to diarylated hydantoin.

Since their discovery by Adolf von Baeyer in 1861,1 imidazolidine-2,4-diones, more commonly known as hydantoins, have become a major scaffold with applications in many areas of science.2 Indeed, in addition to their occurrence in some natural products3 and use in organic synthesis,1 coordination chemistry,5 polymer science,6 and in the design of molecular switches, they had a deep impact in medicinal chemistry and agrochemistry.7 The most famous and representative hydantoin drugs8 include Sano-first-Aventis’ anti-androgen nilutamide, Pfizer’s anticonvulsant fosphenytoin, and Shionogi’s antibacterial nitrofurantoin 3 (Figure 1). Various clinical candidates based on the hydantoin skeleton have in addition been recently reported, Bristol-Myers Squibb’s anti-psoriasis BMS-587101 4 and Galapagos’ anti-cachexia GLGP-0492 5 being representative examples. Hydantoin derivatives such as thiodyantoin have in addition also revealed to be important in healthcare, as highlighted with Medivation/Astellas’ anticancer drug enzalutamide 6.4 During the past decade, the interest for hydantoin has not declined, which resulted in more than 3000 publications and patents. This has stimulated many efforts for the development of synthetic routes to hydantoin: in addition to being efficient, reliable, and short, they moreover need to be highly modular in a diversity-oriented approach. Classical synthetic pathways to hydantoin such as the Read,9 Bucherer-Bergs,10 and Blitz11 reactions indeed all suffer from limitations, and a variety of alternative processes have been reported over the years. However, among all classes of hydantoin, N-arylated ones, that are of particular interest in medicinal chemistry, are not trivial to access using classical methods, notably in terms of the starting materials required. An interesting strategy that would, in addition to involving a limited number of steps from readily available starting materials, be especially relevant for structural diversification, would be based on direct N-arylation of the bare hydantoin scaffold. For some reasons, this attractive approach to N-aryl-hydantoin has been mostly restricted to nucleophilic aromatic substitutions and barely investigated.12–14 We report in this manuscript a set of efficient procedures for the selective arylation of hydantoin at the two nitrogen atoms.

Copper-Mediated N3-Arylation of Hydantoin. Indeed, based on our combined interests in copper-catalysis15,16 and process chemistry,17 we became interested in developing general processes for the arylation of hydantoin at the two nucleophilic nitrogen atoms. We initiated our studies by carefully investigating the scope of the copper-mediated arylation at N3, a reaction that is best performed under ligand-free conditions in the presence of stoichiometric copper(I) oxide,12b–d most certainly due to the starting hydantoin acting as supporting ligands that can in addition

Figure 1. Representative (thio)hydantoin drugs and clinical candidates.
result in the formation of catalytically inactive copper complexes in the presence of catalytic amounts of copper(1) only. Results from these studies are shown in Figure 2.

As illustrated with results from Figure 2, the arylation at N3 was found to be rather general because upon simple reaction with one equivalent of copper(I) oxide and aryl iodides 7 in DMF at 150 °C for 14 h without an additional base, a range of hydantoins could be readily and selectively arylated at N3, providing the corresponding N3-aryl-hydantoins 9a−n that could be isolated in good to excellent yields. The reaction was found to proceed smoothly with a range of aryl iodides, regardless of their electronic properties, and a variety of hydantoins could be arylated under these conditions. The substitution pattern of the starting hydantoin was, however, found to have a significant impact on the selectivity of the reaction starting from hydantoins unsubstituted at N1. Indeed, while 5,5-disubstituted hydantoins were selectively arylated at N3 in all cases, removing one of these substituents led to significant competing arylation at N1, as demonstrated with the isolation of 9m and 9m′ in a ca. 2:1 ratio. The absence of substituents at this position favored the N1-arylation, N1-phenyl-hydantoin 9n being now obtained with significant amounts of diarylated product 9n′′. Gratifyingly, the reaction was successfully extended to the use of aryl bromides, as demonstrated with the arylation to 9o−r isolated in fair to good yields.

**Copper-Catalyzed N1-Arylation of Hydantoins.** After briefly studying the scope of the arylation at N3, we then moved to the more challenging N1-arylation. To make sure aryl bromides could be used in this transformation, the optimization was performed using 1.2 equiv of aryl bromide 10 and sterically hindered hydantoin 9f, the resulting N1-arylated product 11a being an oxygenated analogue of enzalutamide 6. These model substrates were therefore reacted with 20 mol % of copper(I) iodide and 40 mol % of various ligands in the presence of 2 equiv of potassium carbonate in toluene at 110 °C for 64 h: results from these studies are shown in Figure 3. Most ligands commonly used in copper-catalyzed cross-coupling reactions, including 2,2,6,6-tetramethyl-3,5-heptanediene L1, proline L2, 1,2-dimethylimidazole L3, 2,2′-bipyridine L4, and 1,10-phenanthroline L5, failed to promote the arylation, most certainly because of catalyst deactivation due to multiple coordination of the starting hydantoin, as suggested by its nontotal recovery. Except for TMEDA, diamine ligands turned out to be more efficient, trans-N,N′-dimethylcyclohexane-1,2-diamine (Me2CyDA) being by far the most efficient and promoting the coupling to 11a in 61% yield, a yield that could be further improved to 70% by using 1.4 equiv of aryl bromide 10. As for the reaction time, it could be reduced to 48 h without affecting the yield. Further evaluation of different copper sources (CuBr, CuCl, CuTC, CuOAc, Cu(CH3CN)4PF6), bases (K3PO4, Cs2CO3), solvents (dioxane, acetonitrile, DMF, DMSO) and additives (NaI) did not allow a significant further improvement.

Having these optimized conditions in hand, we next turned our attention to the study of the scope and limitations of the N1-arylation using representative hydantoins 12 and aryl halides 7 (Figure 4). Gratifyingly, the reaction scope was found to be especially broad, the arylation proceeding smoothly with electron-rich (11b−d) and electron-poor (11e−g) aryl bromides. It could be extended to the introduction of heteroaryl substituents such as a thiophene (11j), a pyridine (11k), and a benzofuran (11l), the main limitation being the absence of reactivity starting with ortho-substituted aryl bromides (11i). Not surprisingly, aryl iodides performed equally well, and similar trends were observed with...
these reagents. The nature of the substituent(s) at C5 on the starting hydantoin was found to have little effect on the reaction outcome, as demonstrated with the arylation to 11s–v which all proceeded smoothly. The arylation to 11t is in addition quite remarkable due to the high steric hindrance close to the reacting center that still did not inhibit the arylation. Finally, it should be noted that various functional groups such as an ether (11d and p), an ester (11e and v), a ketone (11f), and a nitro (11r) were shown to be compatible with the reaction conditions.

Interestingly, the N3-aryl-hydantoins 9 resulting from the first arylation were also shown to be excellent substrates for the copper-catalyzed N1-arylation, as highlighted in Figure 5. Our two procedures therefore enable clean, selective, and efficient iterative arylations to N1, N3-diaryl-hydantoins 11a and w–ad, attractive scaffolds in medicinal chemistry, and facilitate diversification by a simple modulation of the two aryl groups introduced.

Copper-Mediated Iterative Arylations of Hydantoins on Multigram Scales. In a final effort to demonstrate the synthetic potential of our procedures, a scale-up of the iterative arylations was finally explored. As highlighted in Scheme 1, this turned out to be especially efficient, the first copper-mediated ligand- and base-free arylation of 8a with 13 providing the desired N3-arylated product 9f in 93% on a 84 g scale, using simple purification by precipitation and successive washes with DMF, aqueous ammonia, and water. The second arylation at N1 was undertaken on a 50 g scale using iodobenzene 14 as the arylation agent and gave, after treatment with a mixture of silica and Carcel, filtration, reslurry in a mixture of toluene and heptane, and filtration, the desired doubly arylated hydantoin 11aa with 82% yield, therefore demonstrating the robustness of the sequence.

C4-Selective Thionation of Diarylhydantoins. We finally turned our attention to the extension of these procedures to the arylations of thiohydantoins: despite extensive trials, we could not find conditions enabling these arylation, which might be due to competing complexation of copper by these substrates, which are excellent ligands for copper. Considering in addition that thiohydantoins are known to coordinate to copper by the sulfur atom, their arylation might proceed at sulfur rather than nitrogen. To circumvent this problem, the regioselective thionation of N1, N3-diphenylhydantoin 11m with various reagents was examined: of all reagents evaluated, phosphorus pentasulfide P2S5 was found the most efficient and enabled a clean and C4-selective thionation to 15 (Scheme 2).19

Conclusions. In conclusion, we developed and studied a set of two efficient and broadly applicable procedures for the
N-arylation of hydantoins at the two nitrogen atoms. The first one relies on the use of stoichiometric amounts of copper(I) oxide under ligand- and base-free conditions and enables a clean and regioselective arylation at the N3 nitrogen atom, while the second one is based on the use of catalytic amounts of copper(I) iodide and trans-N,N'-dimethylcyclohexane-1,2-diamine and promotes arylation at the N1 nitrogen atom. The scope of these two procedures has been shown to be quite broad, and they are both tolerant to a range of functional groups. Moreover, they rely on simple copper salts and ligands, and their robustness on multigram scale was demonstrated. Importantly, the combination of these two procedures affords a straightforward and general entry to diarylated hydantoins, which are important scaffolds in medicinal chemistry.

### EXPERIMENTAL SECTION

#### General Information

All reactions were carried out in oven-dried glassware under an argon atmosphere employing standard techniques in handling air-sensitive materials unless otherwise stated.

All reagents and solvents were reagent grade. N,N-Dimethylformamide (99.8%, Extra Dry over Molecular Sieve, AcroSeal) and toluene (99.5%, Extra Dry over Molecular Sieve, AcroSeal) were purchased from ACROS Organics and used as supplied.

#### General Procedure

A1 5m L

A2 10m L

#### Scheme 2. C4-Selective Thionation of a N3,N3-Diaryldydhantoin

![Diagram of Scheme 2](image)

#### 5,5-Dimethyl-3-phenylhydantoin 9a

Yield: 69% (280 mg, 1.37 mmol). White solid. Solvent system for flash column chromatography: petroleum ether/EtOAc: 60/40. This compound has been previously reported.20

#### 3-(1,1'-Biphenyl-4-yl)-5,5-dimethylhydantoin 9b

Yield: 87% (404 mg, 1.44 mmol). White solid. Mp: 185 °C; 1H NMR (400 MHz, CDCl3): δ 7.74 (d, J = 8.6 Hz, 2H), 7.72–7.68 (m, 2H), 7.55 (d, J = 8.6 Hz, 2H), 7.53–7.43 (m, 3H), 7.38 (t, J = 7.4 Hz, 1H), 1.52 (s, 6H); 13C{1H} NMR (100 MHz, CDCl3): δ 177.1, 155.2, 141.1, 141.0, 133.0, 129.8, 128.4, 127.8, 127.6, 58.9, 25.4; IR (neat): νmax 1713, 1428, 1303, 1144, 837, 768 cm⁻¹; ESI HRMS m/z calculated for C18H14N2O2 [M + H]⁺ 281.1285, found 281.1290.

#### 5,5-Dimethyl-3-(3-methoxyphenyl)hydantoin 9c

Yield: 73% (344 mg, 1.47 mmol). Solvent system for flash column chromatography: cyclohexane/EtOAc: 60/40; Beige solid, Mp: 106 °C; 1H NMR (400 MHz, CDCl3): δ 7.36 (app, t, J = 8.2 Hz, 1H), 7.12–7.01 (m, 1H), 6.99 (d, J = 7.9 Hz, 1H), 6.96–6.90 (m, 2H), 3.81 (br, s, 3H), 1.49 (br, s, 6H); 13C{1H} NMR (100 MHz, CDCl3): δ 176.4, 160.1, 155.8, 132.7, 129.8, 118.6, 114.2, 112.1, 58.7, 55.2; IR (neat): νmax 2976, 1716, 1418, 1151, 1043, 720 cm⁻¹; ESI HRMS m/z calculated for C18H14N2O2 [M + H]⁺ 235.1077, found 235.1080.

#### 5,5-Dimethyl-3-(4-trifluoromethylphenyl)hydantoin 9d

Yield: 88% (479 mg, 1.76 mmol). Off-white solid, Mp: 179 °C; 1H NMR (300 MHz, acetone-d6): δ 7.79 (d, J = 21.3 and 8.6 Hz, 4H), 7.59 (br, s, 1H), 1.52 (s, 6H); 13C{1H} NMR (100 MHz, acetone-d6): δ 176.8, 154.6, 137.4, 129.4 (q, JCF = 32.5 Hz), 127.3, 126.4 (q, JCF = 39.9 Hz), 123.8, 59.0, 25.3; IR (neat): νmax 2361, 1732, 1719, 1410, 1324, 1140, 1327, 1132, 1106, 836, 709 cm⁻¹; ESI HRMS m/z calculated for C18H14F2N2O2 [M + H]⁺ 273.0845, found 273.0849.

#### 5,5-Dimethyl-3-(4-nitrophenyl)hydantoin 9e

Yield: 80% (397 mg, 1.59 mmol). Beige solid, Mp: 168 °C; 1H NMR (400 MHz, CDCl3): δ 8.35 (d, J = 9.2 Hz, 2H), 7.86 (d, J = 9.2 Hz, 2H), 7.68 (br, s, 1H), 1.54 (s, 6H); 13C{1H} NMR (100 MHz, acetone-d6): δ 176.7, 154.3, 147.0, 139.6, 127.1, 124.6, 59.0, 25.3; IR (neat): νmax 2360, 1732, 1719, 1514, 1342, 1135, 841, 726 cm⁻¹; ESI HRMS m/z calculated for C18H14N2O2 [M + Na]⁺ 255.1104, found 255.1109.

#### 5,5-Dimethyl-3-(4-cyano-4-phenylphenyl)hydantoin 9f

Yield: 82% (68 g, 22.9 mmol). White solid. Solvent system for flash column chromatography: cyclohexane/EtOAc: 90/10. This compound has been previously reported.21

#### 1-Methyl-3-phenylhydantoin 9g

Yield: 54% (207 mg, 1.09 mmol). Off-white solid. Solvent system for flash column chromatography: petroleum ether/EtOAc: 50/50. This compound has been previously reported.22

#### 1-Butyl-3-phenylhydantoin 9h

Yield: 58% (270 mg, 1.16 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 70/30. This compound has been previously reported.23

#### 5-[(Ethylamino)carbonyl]-3-phenylhydantoin 9i

Yield: 68% (298 mg, 1.36 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 70/30; White solid, Mp: 114 °C; 1H NMR (400 MHz, CDCl3): δ 7.50–7.44 (m, 2H), 7.42–7.34 (m, 3H), 6.97

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**Note:**

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(br. s, 1H), 1.93 (A of ABX, syst. J = 14.7 and 7.4 Hz, 1H), 1.71 (B of ABX syst. J = 14.7 and 7.4 Hz, 1H), 1.47 (s, 3H), 0.94 (X of ABX syst. J = 7.4 Hz, 3H); 13C{1H} NMR (100 MHz, CDCl3): δ 176.1, 156.4, 131.7, 129.2, 128.3, 126.3, 62.4, 31.2, 23.7, 7.9; IR (neat): νmax 2934, 2368, 1714, 1504, 1412, 1134, 846, 709 cm⁻¹; ESI HRMS m/z calc for C₉H₉NO₂ [M + H⁺]: 199.1218, found 199.1143.

5,5-Dimethyl-1-(4-methylcarbamoylphenyl)-3-(3-trifluoromethoxyphenyl)hydantoin 11a Yield: 70% (2.9 g, 6.38 mmol). White solid. Solvent system for flash column chromatography: cyclohexane/eton/ioc: 50/50. This compound has been previously reported. 26

5,5-Dimethyl-1-(3,5-dimethyl-4-oxo-phenyl)hydantoin 11b Yield: 75% (251 mg, 0.76 mmol). Solvent system for flash column chromatography: cyclohexane/EtOAc: 90/10; Off-white solid, Mp: 141 °C; H NMR (600 MHz, CDCl3): Δ δ 7.53–7.49 (m, 2H), 7.49–7.45 (m, 4H), 7.39–7.35 (app. t, J = 7.3 and 1.4 Hz, 1H), 7.25–7.22 (d, J = 8.6 Hz, 2H), 1.55 (s, 6H), 1.35 (s, 9H); 13C{1H} NMR (150 MHz, CDCl3): δ 175.4, 154.1, 151.7, 132.0, 131.2, 129.1, 128.6, 128.1, 126.6, 126.2, 63.5, 34.8, 31.4, 24.2; IR (neat): νmax 2968, 1715, 1396, 1204, 1138, 766 cm⁻¹; ESI HRMS m/z calc for C₉H₉NO₂ [M + H⁺]: 337.1911, found 337.1913.

5,5-Dimethyl-1-(naphthalen-2-yl)-3-phenylhydantoin 11c Yield: 91% (300 mg, 908 μmol). Solvent system for flash column chromatography: cyclohexane/EtOAc: 80/20; Beige solid, Mp: 163 °C; H NMR (600 MHz, CDCl3): Δ δ 7.95 (d, J = 8.7 Hz, 1H), 7.92–7.85 (m, 2H), 7.74 (d, J = 2.0 Hz, 1H), 7.58–7.54 (m, 4H), 7.52–7.49 (m, 2H), 7.43 (dd, J = 8.7 and 2.1 Hz, 1H), 7.39 (tt, J = 7.4 and 1.3 Hz, 1H), 1.62 (s, 6H); 13C{1H} NMR (150 MHz, CDCl3): δ 175.3, 154.2, 133.6, 133.0, 131.9, 131.6, 129.6, 129.1, 128.2, 128.1, 127.9, 127.9, 127.0, 126.9, 126.6, 126.3, 63.8, 24.4; IR (neat): νmax 2981, 1716, 1504, 1401, 1201, 1143, 779 cm⁻¹; ESI HRMS m/z calc for C₁₉H₁₉NO₂ [M + H⁺]: 341.1441, found 331.1440.

5,5-Dimethyl-3-phenyl-1-(4-trifluoromethoxyphenyl)hydantoin 11d Yield: 96% (349 mg, 958 μmol). Solvent system for flash column chromatography: cyclohexane/EtOAc: 95/5; Pale yellow solid, Mp: 96 °C; H NMR (400 MHz, CDCl3): Δ δ 7.40–7.34 (m, 4H), 7.34–7.31 (m, 2H), 7.32–7.27 (m, 2H), 5.33 (s, 2H), 4.04 (s, 2H), 3.82 (s, 3H); 13C{1H} NMR (150 MHz, CDCl3): δ 174.8, 153.8, 148.8, 132.6, 131.7, 130.9, 129.0, 128.2, 126.1, 121.9, 120.4 (q, J = 25.8 Hz), 63.5, 24.0; 19F NMR (376 MHz, CDCl3): δ −68.3 (s); IR (neat): νmax 1739, 1715, 1506, 1411, 1266, 1200, 1156, 776 cm⁻¹; ESI HRMS m/z calc for C₁₉H₁₉F₄NO₂ [M + H⁺]: 365.1108, found 365.1109.

5,5-Dimethyl-1-(4-methylcarbamoylphenyl)-3-phenylhydantoin 11e Yield: 68% (231 mg, 682 μmol). Solvent system for flash column chromatography: cyclohexane/EtOAc: 80/20; White solid, Mp: 101 °C; H NMR (400 MHz, CDCl3): Δ δ 8.03 (s, 1H), 7.89 (dd, J = 7.4 and 8.0 Hz, 2H), 7.66 (d, J = 8.7 Hz, 2H), 7.61 (s, 1H), 7.45 (s, 1H), 6.82 (s, 1H); 13C{1H} NMR (100 MHz, CDCl3): δ 176.9, 154.9, 148.5, 132.7, 128.8, 122.1, 121.4 (q, J = 25.55 Hz), 90.0, 25.3; 19F NMR (376 MHz, CDCl3): δ −63.2 (s); IR (neat): νmax 2977, 1708, 1414, 1276, 1201, 1112, 769 cm⁻¹; ESI HRMS m/z calc for C₁₉H₁₉NO₂ [M + H⁺]: 339.1339, found 339.1341.

1-(Acetylphenyl)-5,5-dimethyl-3-phenylhydantoin 11f Yield: 95% (305 mg, 947 μmol). Solvent system for flash column chromatography: cyclohexane/EtOAc: 70/30; Yellow solid, Mp: 138 °C; H NMR (400 MHz, CDCl3): Δ δ 8.06–8.01 (d, J = 8.4 Hz, 2H), 7.51–7.44 (m, 4H), 7.41–7.35 (m, 1H), 3.93 (s, 3H), 1.59 (s, 6H); 13C{1H} NMR (100 MHz, CDCl3): δ 174.8, 166.3, 153.8, 138.9, 131.6, 130.9, 129.7, 129.1, 128.4, 127.8, 126.2, 63.9, 26.7, 24.4; IR (neat): νmax 2969, 1710, 1675, 1405, 1363, 1202, 766 cm⁻¹; ESI HRMS m/z calc for C₁₉H₁₉NO₂ [M + H⁺]: 323.1390, found 323.1399.

1-(3,5-Difluorophenyl)-5,5-dimethyl-3-phenylhydantoin 11g Yield: 84% (267 mg, 847 μmol). Solvent system for flash column chromatography: cyclohexane/EtOAc: 95/5; Beige solid, Mp: 122 °C; H NMR (400 MHz, CDCl3): Δ δ 7.51–7.45 (m, 4H), 7.43–7.36 (m, 1H); 6.96 (app. dd, J = 7.7 and 2.2 Hz, 2H), 6.86 (app. tr, J = 8.8 and 2.3 Hz, 1H), 1.59 (s, 6H); 13C{1H} NMR (100 MHz, CDCl3): δ 174.5, 163.3 (d, J = 249.6 Hz), 163.2 (d, J = 249.5 Hz), 153.6, 136.9 (app. t, J = 12.4 Hz), 131.5, 129.2, 128.5, 126.2, 111.4 (d, J = 27.1 Hz), 111.4 (d, J = 11.7 Hz), 104.0 (app. t, J = 25.2 Hz), 63.9, 24.2;
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5,5-Dimethyl-1-(4-nitrophenyl)-3-phenylhydantoin 11r. Yield: 65% (213 mg, 654 µmol). Solvent system for flash column chromatography: cyclohexane/EtOAc: 70:30; Yellow solid, Mp: 131 °C; 1H NMR (400 MHz, CDCl3): δ 8.30–8.23 (m, 2H), 7.62–7.57 (m, 2H), 7.50–7.44 (m, 4H), 7.42–7.35 (m, 1H), 1.63 (br, s, 6H); 13C{1H} NMR (100 MHz, CDCl3): δ 174.7, 153.5, 146.3, 140.9, 131.3, 129.1, 128.5, 127.3, 126.1, 124.8, 64.0, 24.3; IR (neat): νmax 1716, 1515, 1407, 1334, 1198, 795, 751 cm⁻¹; ESI HRMS m/z calcd for C18H17N3O2 [M + H]+ 326.1135, found 326.1133.

5-Ethyl-5-methyl-1,3-diphenylhydantoin 11s. Yield: 73% (106 mg, 365 µmol). Solvent system for flash column chromatography: cyclohexane/EtOAc: 90:10; White solid, Mp: 129 °C; 1H NMR (400 MHz, CDCl3): δ 7.51–7.43 (m, 6H), 7.42–7.33 (m, 4H), 7.20 (A of ABX syst., J = 14.6 and 7.4 Hz, 1H), 1.55 (s, 3H), 1.05 (X of ABX syst., J = 7.4 Hz, 3H); 13C{1H} NMR (100 MHz, CDCl3): δ 174.6, 154.7, 154.4, 134.1, 131.8, 129.6, 129.1, 128.3, 128.2 (2C), 126.3, 67.6, 29.9, 23.7, 8.2; IR (neat): νmax 2934, 1712, 1494, 1412, 1374, 1190, 762, 693 cm⁻¹; ESI HRMS m/z calcd for C17H16N3O3 [M + Na]+ 317.1260, found 317.1275.

5,5-Dimethyl-1-(3-trifluoromethylphenyl)-3-phenylhydantoin 11t. Yield: 97% (338 mg, 970 µmol). White solid. Solvent system for flash column chromatography: cyclohexane/EtOAc: 80:20. This compound has been previously reported.14

1,3-Diphenyl-5-methylhydantoin 11u. Yield: 91% (63 mg, 237 µmol). Off-white solid. Solvent system for flash column chromatography: cyclohexane/EtOAc: 85:15. This compound has been previously reported.14

3-[1',1'-Biphenyl-4-yl]-5,5-dimethyl-1-phenylhydantoin 11w. Yield: 78% (279 mg, 782 µmol). Solvent system for flash column chromatography: cyclohexane/EtOAc: 85:15; White solid, Mp: 115 °C; 1H NMR (400 MHz, CDCl3): δ 7.73–7.68 (m, 2H), 7.64–7.59 (m, 4H), 7.52–7.41 (m, 5H), 7.40–7.33 (m, 3H), 1.58 (s, 6H); 13C{1H} NMR (100 MHz, CDCl3): δ 175.3, 154.0, 141.2, 140.4, 134.2, 131.0, 129.7, 129.1, 128.9, 128.7, 127.8, 127.7, 127.3, 126.4, 63.6, 24.3; IR (neat): νmax 2982, 1710, 1445, 1383, 1216, 1017, 747 cm⁻¹; ESI HRMS m/z calcd for C26H20N3O4 [M + Na]+ 393.1458, found 393.1459.

5,5-Dimethyl-1-(3-methoxyphenyl)-3-phenylhydantoin 11x. Yield: 97% (193 mg, 622 µmol). Solvent system for flash column chromatography: cyclohexane/EtOAc: 30:70; White solid, Mp: 58 °C; 1H NMR (400 MHz, CDCl3): δ 7.43–7.36 (m, 2H), 7.35–7.31 (m, 2H), 7.13–7.09 (m, 1H), 7.08 (t, J = 2.2 Hz, 2H), 6.92 (ddd, J = 8.4, 2.5, and 0.7 Hz, 1H), 3.81 (s, 3H), 1.54 (s, 6H); 13C{1H} NMR (100 MHz, CDCl3): δ 175.1, 159.9, 153.8, 134.0, 132.8, 129.6, 129.5, 129.0, 128.5, 118.3, 114.3, 111.7, 63.4, 55.4, 24.0; IR (neat): νmax 2935, 1718, 1498, 1407, 1379, 1200, 1151, 765 cm⁻¹; ESI HRMS m/z calcd for C17H17N3O3 [M + H]+ 295.1087, found 295.1087.

5,5-Dimethyl-1-(3-trifluoromethylphenyl)-3-phenylhydantoin 11y. Yield: 99% (158 mg, 487 µmol). Solvent system for flash column chromatography: cyclohexane/EtOAc: 80:20; Yellow solid, Mp: 131 °C; 1H NMR (400 MHz, CDCl3): δ 8.33 (d, J = 9.2 Hz, 2H), 7.85 (d, J = 9.2 Hz, 2H), 7.53–7.43 (m, 3H), 7.34–7.30 (m, 2H), 1.57 (s, 6H); 13C{1H} NMR (100 MHz, CDCl3): δ 174.7, 153.0, 146.5, 137.8, 133.5, 132.9, 129.2 (2C), 126.0, 124.4, 63.7, 24.3; IR (neat): νmax 2936, 2362, 1716, 1517, 1411, 1342, 1281, 1246, 763, 697 cm⁻¹; ESI HRMS m/z calcd for C18H17F3N3O3 [M + H]+ 326.1135, found 326.1148.
chromatography: cyclohexane/ETOC: 90/10; White solid, Mp: 135 °C; 1H NMR (400 MHz, CDCl3): δ 7.73 (app, s, 4H), 7.51–7.40 (m, 3H), 7.35–7.30 (m, 2H), 1.56 (s, 6H). (1Cl) NMR (100 MHz, CDCl3): δ 174.9, 153.3, 135.2, 133.7, 129.8 (J = 35.8 Hz), 129.7, 129.1, 129.0, 128.8, 128.3, 123.4 (q, J = 33.1 Hz), 133.2, 130.0, 129.4, 129.2, 128.3, 124.3 (q, J = 272.3 Hz), 63.6, 24.2; IR (neat): νmax 2986, 2232, 1719, 1404, 1313, 1131, 850, 691 cm−1; ESI HRMS m/z calcd for C18H16F3N2O3 [M + H]+ 365.1108, found 365.1120.

N'-Arylation of 5,5-Dimethyl-3-(3-trifluoromethyl-4-cyanophenyl)hydantoin 9f. A 1 L four-necked round-bottom flask equipped with a condenser, a mechanical stirrer, and a temperature probe was charged with 5,5-dimethyl-3-(3-trifluoromethyl-4-cyanophenyl)hydantoin 9f (50.0 g, 168 mmol), copper iodide (6.40 g, 33.6 mmol), potassium carbonate (46.5 g, 336 mmol), and toluene (240 mL). The flask was fitted with a glass stopper and was then flushed with nitrogen at 22 ± 3 °C before trans-N,N'-dimethylcyclohexane-1,2-diamine (9.60 g, 67.3 mmol) was added over ca. 2 min. The reaction mixture turned blue, and a slight exotherm (up to 26 °C) was observed (Picture 1, Supporting Information). Iodobenzene (48.0 g, 235 mmol) was added over 5 min (Picture 2, Supporting Information), and the mixture was then heated to reflux (110 °C, Picture 3, Supporting Information) and stirred for 24 h (the mixture turns green upon heating, Picture 4, Supporting Information). TLC (heptane/ethyl acetate: 60/40) showed complete consumption of the starting material (Picture 5, Supporting Information). The temperature was adjusted to 22 ± 3 °C, and ethyl acetate (340 mL) was added followed by silica (50.0 g) and Clarcel (50.0 g). The mixture was stirred for 15 min and filtered through a Büchner (Picture 6, Supporting Information). The cake was copiously washed with ethyl acetate (1650 mL). The filtrate was concentrated to low volume at 40 °C under vacuum to yield a brown residue (117 g). Toluene (340 mL) and heptane (200 mL) were added, and the resulting suspension was stirred for 1 h at 22 ± 3 °C and then for 1 h at 2 ± 3 °C (Picture 7, Supporting Information). The cake was washed twice with a cold mixture of toluene (30 mL) and heptane (20 mL) (Picture 8, Supporting Information). The wet product (98.7 g) was dried under vacuum at 50 °C for 18 h to yield 5,5-dimethyl-1-phenyl-3-(3-trifluoromethyl-4-cyanophenyl)hydantoin 11z as an off-white solid (51.3 g, 137 mmol, 82%).

C4-Selective Thionation of 5,5-Dimethyl-1,3-diphenylhydantoin. 5,5-Dimethyl-1,3-diphenyl-4-thiohydantoin 15. In a pressure tube, 5,5-dimethyl-1,3-diphenylhydantoin 11l (140 mg, 0.50 mmol) was dissolved in toluene (2 mL) before adding phosphorus pentasulfide (111 mg, 0.50 mmol). The pressure tube was flushed with argon and closed with a Teflon-coated screw cap before the reaction mixture was heated at 120 °C for 18 h. The mixture was then cooled to room temperature, quenched with a 1 M aqueous solution of hydrochloric acid, and extracted with EtOAc. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated. The crude residue was purified by flash column chromatography over silica gel (cyclohexane/ETOC: gradient from 90/10 to 80/20) to give the desired 5,5-dimethyl-1,3-diphenyl-4-thiohydantoin, obtained as a white solid and a single regiosomer (85 mg, 0.29 mmol, 57%). The regioselectivity of the thionation and the structure of this compound was assigned on the basis of 13C NMR chemical shifts reported for enzulamide.15 The two regioisomers were reported in 1983 but had been missigned.19 Mp: 138 °C; 1H NMR (400 MHz, CDCl3): δ 7.57–7.43 (m, 8H), 7.38–7.35 (m, 2H), 1.67 (s, 6H); 13C NMR (100 MHz, CDCl3): δ 208.9, 154.2, 134.5, 134.3, 129.6, 129.2 (3C), 128.9, 127.7, 72.3, 28.1; IR (neat): νmax 2965, 1405, 1335, 1297, 1194, 1197, 1199, 1151, 767, 697 cm−1; ESI HRMS m/z calcd for C17H16F3N2OSNa [M + Na]+ 319.0876, found 319.0884.

### Multigram Scale Procedures

N'-Arylation of 4,4-Dimethylhydantoin 8a. A 2 L four-necked round-bottom flask equipped with a condenser, a mechanical stirrer, and a temperature probe was charged with 4-iodo-2-trifluoromethoxononilene (90.0 g, 303 mmol), copper(I) oxide (97% grade, 44.7 g, 303 mmol), and N,N-dimethylformamide (873 mL). 5,5-Dimethyldihydantoin 8a (58.2 g, 455 mmol) was added, and the flask was fitted with a glass stopper. The reaction mixture was stirred at 150 °C for 16 h. After being cooled to room temperature, the red suspension was filtered through a cardboard filter and washed with N,N-dimethylformamide (58 mL). The filtrate was concentrated under reduced pressure and dissolved in N,N-dimethylformamide (58 mL), and the green suspension was transferred into an addition funnel. A 1 L four-necked round-bottom flask equipped with a condenser, a mechanical stirrer, a temperature probe, and the latter addition funnel was charged with 233 mL of demineralized water. The green suspension was added over 10 min and stirred for 30 min before adding a 28% aqueous ammonia solution (111 mL) over 5 min. The resulting mixture was stirred for 30 min. The precipitate was collected by filtration, washed with water (3 × 58 mL), and then dried under high vacuum at 40 °C for 72 h to yield 5,5-dimethyl-3-(3-trifluoromethyl-4-cyanophenyl)hydantoin 9f as a white solid (83.6 g, 281 mmol, 93%).

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b02284. Pictures of the different stages of the multigram scale N'-arylation and copies of NMR spectra (PDF)

Primary NMR data files (ZIP)
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