Study on the Lithiation Reaction of 3-Diisopropylcarbamoyl-
N-pivaloylphenylethylamine

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Abstract
As a continuation of our earlier studies on the lithiation-based synthesis of 8-methoxy-, 8-fluoro- and 8-chloro-3,4-dihydroisoquinoline, a similar approach was investigated for the preparation of the 8-diisopropylcarbamoyl congener. The corresponding N-pivaloyl phenylethylamine key intermediate was prepared via four new bifunctional intermediates in high overall yield. Lithiation of this intermediate followed by quenching with dimethylformamide led to a mixture: beside the desired compound containing the formyl moiety in the common ortho position of the two aromatic substituents, the isomer formylated in the other ortho position of the carbamoyl moiety was surprisingly obtained as the major product. The crude mixture could finally be transformed under acidic conditions to the target compound, 8-diisopropylcarbamoyl-substituted 3,4-dihydroisoquinoline, albeit in a low yield.

Keywords
isoquinoline, lithiation, reduction, cyclization, bromination

1 Introduction
Isoquinolines and their partly saturated derivatives (i.e., dihydro- and tetrahydroisoquinolines) represent an important family of natural and synthetic compounds exhibiting biological activity. The significance of 8-substituted congeners is also demonstrated by the marketed antidepressant drug nomifensine (1, Fig. 1), a norepinephrine–dopamine reuptake inhibitor that was launched as an antidepressant drug exhibiting no sedative effects [1]. Furthermore, 1,8-disubstituted 1,2,3,4-tetrahydroisoquinolines (2, Fig. 1) proved to be potent calcium channel blockers synthesized for the treatment of chronic pain [2].

The observed biological activity of isoquinoline derivatives substituted at position 8 of the aromatic ring initiated a work at our laboratory aiming at the development of efficient synthetic methods for the preparation of 8-substituted 3,4-dihydroisoquinolines and for their further transformation to various 8-substituted and 1,8-disubstituted 1,2,3,4-tetrahydroisoquinolines. A comprehensive literature search revealed that the syntheses of tetrahydroisoquinolines bearing a single substituent on the benzene ring at position 8 necessitate various synthetic solutions that cannot be generalized. These literature approaches were summarized in our recent publications [3, 4].

We anticipated that N-pivaloyl-phenylethlamines exhibiting a directed metalation group (DMG) in the meta position could be suitable starting compounds for the elaboration of a general procedure, due to a regioselective lithiation in the common ortho position of the two aromatic substituents. As a first example, a short and efficient synthesis of 8-methoxy-3,4-dihydroisoquinoline (3a) was reported [5]. Lithiation of N-pivaloyl-3-methoxyphenylethylamine (4a) with butyllithium (BuLi) in diethyl ether (DEE) at ambient temperature occurred at the common ortho site of the substituents (5a), and subsequent treatment with dimethylformamide (DMF) led to formyl derivative 6a (Scheme 1). Later, we succeeded in extending the reaction sequence to...
N-pivaloyl-3-fluorophenylethylamine [3]. In the metalation step of 4b with BuLi, significant modifications had to be introduced. It was performed at −78 °C in order to prevent aryne formation by LiF elimination. Due to the poor solubility of compound 5b in DEE at this low temperature, tetrahydrofuran (THF) was used as the solvent. Subsequent quenching with DMF afforded formyl derivative 6b.

The easy availability of compounds 6 allowed the syntheses of 8-substituted-isoquinolines simpler than hitherto known. Acid-catalyzed cyclization of compounds 6 accompanied by the loss of the pivaloyl moiety resulted in the corresponding 8-substituted 3,4-dihydroisoquinolines 3, which are suitable starting compounds for the preparation of a wide variety of 8-substituted-isoquinolines and 1,2,3,4-tetrahydroisoquinolines.

In continuation of these studies, we decided to extend this approach to the synthesis of 8-chloro-3,4-dihydroisoquinoline (3c, Scheme 2). According to our earlier studies in other families of compounds [6-8] and to other literature analogies, [9-11] a complimentary directing effect of the two substituents is expected in the lithiation reaction of N-pivaloyl-3-chlorophenylethylamine (4c). To our surprise, lithiation of N-pivaloyl-3-chlorophenylethylamine (4c) with BuLi in THF at −78 °C, followed by treatment with DMF gave a product mixture formylated rather in the benzylic position of the side chain (7) than at the required ring position (6c, Scheme 2), with a molar ratio 2.5 : 1 for 7 and 6c, respectively [4]. Acidic treatment of this crude mixture afforded target compound 3c with only 9 % overall yield for the two steps.

### 2 Results and discussion

The aim of the present study was to investigate the extensibility of the simple isoquinoline synthesis for derivatives exhibiting a carboxylic acid or carboxylic acid derivative moiety, as a versatile functional group, at position 8. The key issue is whether we can carry out a regioselective lithiation at the common ortho site of the corresponding starting compound.
There are many options that can be considered when selecting the suitable carboxylic acid derivative DMG in the meta position of N-pivaloylphenylethylamine. The carboxylic acid group itself is an ortho director in lithiation reactions [12]. However, it seems to be unfavorable for us, because a double deprotonation of the starting compound prior to the lithiation reaction is expected to give rise to the formation of a poorly soluble dianion. A similar problem may occur in the case of secondary amide DMG’s [13]. Tertiary amides are also powerful DMG’s. N,N-Diethylbenzamide requires the use of sec-BuLi in the metalation reaction in order to avoid ketone formation. [14, 15] Beak et al. reported ortho-lithiation of N,N-diisopropylbenzamides with BuLi/TMEDA at −78 °C [16]. In the course of our efforts to synthetize variously substituted phthalides we succeeded in performing similar reactions in the absence of TMEDA [7, 17]. Based on this experience we decided to apply N-pivaloylphenylethylamine substituted with N,N-diisopropylcarbamoyl group at the meta position (4d) in our study.

Contrary to 3-methoxy, 3-fluoro- and 3-chlorophenylethylamine, the 3-diisopropylcarbamoyl analogue (8, Scheme 3) is not commercially available, thus it was synthesised starting from 3-methylbenzoic acid (9) in 4 steps (Scheme 3). First, acid 9 was treated with thionyl chloride (SOCl₂) and disopropyl amine [(iPr)₂NH] to give disopropylamide 10, the bromination of which with N-bromosuccinimide (NBS) in the presence of a catalytic amount of azobisisobutyronitrile (AIBN) furnished bromomethyl derivative 11. Nucleophilic substitution with sodium cyanide (NaCN) and subsequent catalytic hydrogenation of nitrile 12 with Raney nickel (Ra-Ni) in methanolic ammonia resulted in phenylethylamine 8 that was acylated with pivaloyl chloride (PivCl) in the presence of triethylamine (Et₃N) giving rise to the formation of key intermediate 4d.

Unfortunately, lithiation of 3-diisopropylcarbamoyl N-pivaloyl derivative 4d under the conditions applied for the 3-fluoro and 3-chloro analogue (BuLi in THF at −78 °C) followed by treatment with DMF did not take place in a regioselective manner. LC-MS analysis of the complex mixture indicated that, beside some unidentified components and the expected formyl compound 6d, another compound was detected as the major isomer (Scheme 4). Upon analogy with the lithiation of N-pivaloyl-3-chlorophenylethylamine

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**Scheme 3** Preparation of N-pivaloyl key intermediate 4d

**Scheme 4** Transformation of N-pivaloyl key intermediate 4d to 3,4-dihydroisoquinoline derivative 3d
(4c, Scheme 2), this major product was thought to be the derivative formylated in the benzyl position of side chain. Nonetheless, after work-up of the crude mixture by flash chromatography, the pending compound surprisingly proved to be derivative 13 that contains a formyl moiety in the sterically less hindered ortho position of the disopropylcarbamoyl group. The structure of 13 was determined by detailed NMR studies (HSQC, HMBC, NOESY).

Despite all our efforts (use of 2 or 3 eq BuLi in THF at −78 °C and at −40 °C with various reaction times; reaction with 3 eq BuLi in diethyl ether at 0 °C and −78 °C; lithiation with 3 eq s-BuLi in THF at −78 °C) to find optimized reaction conditions, the ratio of 6d in the mixture could not be increased, and 6d could not be isolated in a pure form. Nevertheless, acidic treatment of the crude mixture obtained after the lithiation step finally afforded the 8-disopropylcarbamoyl-substituted 3,4-dihydroisoquinoline target compound (3d), albeit in a low yield (3 % calculated for 4d, Scheme 4).

3 Conclusion

The aim of the present study was the elaboration of a synthetic route of 8-disopropylcarbamoyl-substituted 3,4-dihydroisoquinoline, based on the directed ortho-lithiation of the N-pivaloyl phenylethylamine derivative containing a disopropylcarbamoyl moiety in the meta position. In spite of the presence of two DMG groups meta to each other, the lithiation did not preferably take place in the common ortho position. Thus, a mixture was obtained containing the desired regioisomer 6d as a minor component. Finally, the crude mixture could be transformed to the novel substituted 3,4-dihydroisoquinoline 3d in low yield. The new bifunctional intermediates 4d, 8, 11 and 12 can be applied as versatile building blocks in the synthesis of other types of compounds, too, so the significance of the synthetic route described above goes beyond synthesis of compound 3d.

4 Experimental section

All melting points were determined on a Büchi B-540 (Flawil, Switzerland) capillary melting point apparatus and are uncorrected. IR spectra were obtained on a Bruker ALPHA FT-IR spectrometer (Billerica, MA, USA) in KBr pellets or as a film. 1H NMR, 13C NMR, HSQC, HMBC, NOESY and DEPTQ spectra were recorded at 295 K on a Bruker Avance III HD 600 (Billerica, MA, USA) (600 and 150 MHz for 1H and 13C NMR spectra, respectively) spectrometer. CDCl3, was used as the solvent and tetramethylsilane (TMS) as the internal standard. Chemical shifts (δ) and coupling constants (J) are given in ppm and in Hz, respectively. Mass spectra were recorded on a Bruker O-TOF MAXIS Impact mass spectrometer (Billerica, MA, USA) coupled with a Dionex Ultimate 3000 RS HPLC (Sunnyvale, CA, USA) system with a diode array detector. The reactions were followed by analytical thin-layer chromatography on silica gel 60 F254 (Darmstadt, Germany) and HPLC-MS on a Shimadzu LC-20 HPLC equipment (Kyoto, Japan). Purifications by flash chromatography were performed applying a Teledyne Isco CombiFlash® RF system (Thousand Oaks, CA, USA) with Redisep® RF silica flash columns using a hexane–ethyl acetate (EtOAc) or a dichloromethane (DCM)–methanol (MeOH) solvent system. Purification by preparative HPLC was carried out using Phenomenex Gemini-NX C18 column (Torrance, CA, USA, 50×250 mm, d=10 µm, CV=252 mL). All reagents were purchased from commercial sources. Compounds 9 and 10 are known in the literature, while compounds 3d, 4d, 8, 11, 12, 13 are new, and are characterized below.

3-Methyl-1,N,N-bis(propan-2-yl)benzamide (10).

SOCl2 (40.3 mL, 66.1 g, 555 mmol) was added to a solution of 3-methylbenzoic acid (9, 30.2 g, 222 mmol) in toluene (40 mL). After stirring for 4 h at 50 °C, the solvent and SOCl2 were distilled under reduced pressure. The residue was dissolved in toluene (350 mL), and treated with (iPr)2NH (62.2 mL, 44.9 g, 444.1 mmol), and the reaction mixture was cooled with an ice-water bath. After stirring for 2 h at room temperature, the reaction mixture was diluted with water (50 mL). The layers were separated and the aqueous layer was extracted with toluene (2×30 mL). The combined organic layer was dried over MgSO4. The solvent was evaporated to afford the title compound (43.5 g, 90 %) as a pale yellow solid. Mp 59–60 °C (toluene), lit. mp 59–60 °C [18]. IR (KBr): v 2998, 1631, 1340 cm−1. 1H NMR (600 MHz, CDCl3): δ 7.25 (t, J = 7.5 Hz, 1H), 7.17 (d, J = 7.5 Hz, 1H), 7.12 (s, 1H), 7.08 (d, J = 7.5 Hz, 1H), 3.86 (br, 1H), 3.50 (br, 1H), 2.36 (s, 3H), 1.54 (br, 6H), 1.13 (br, 6H) ppm. 13C NMR (150 MHz, CDCl3): δ 171.16, 138.86, 138.21, 129.22, 128.19, 20.65 ppm. HRMS calcd. for C13H25NO ([M+H]+): 220.1696, found 220.1695. Spectral data are in accord with the literature [18].
solvent was evaporated. The residue was purified by flash chromatography (8–20 % EtOAc in hexane) to afford the title compound (30.8 g, 67 %) as a yellow oil. IR (film): ν 3358, 2968, 1629, 1341 cm−1.

1H NMR (600 MHz, CDCl3): δ 7.31 (t, J = 7.5 Hz, 1H), 7.24 (d, J = 7.5 Hz, 1H), 7.20 (s, 1H), 7.18 (d, J = 7.5 Hz, 1H), 7.17 (d, J = 7.5 Hz, 1H), 7.13 (s, 1H), 5.69 (br, 1H), 3.83 (br, 1H), 3.52 (br, 1H), 1.54 (br, 6H), 1.15 (br, 6H) ppm. 13C NMR (150 MHz, CDCl3): δ 170.27, 139.48, 138.75, 129.27, 128.73, 126.16, 125.29, 117.49, 50.99, 45.85, 32.89, 20.68 ppm. HRMS calcd. for C20H21BrNO+ ([M+H]+): 298.0810, found 298.0801.

3-(Cyanomethyl)-N,N-bis(propan-2-yl)benzamide (12). NaCN (6.60 g, 135.6 mmol) was added to a solution of 11 (20.2 g, 67.8 mmol) in DMF (100 mL). After stirring for 4 h at 60 °C, water (40 mL) was added, and the resulting mixture was extracted with EtOAc (3×150 mL). The combined organic layer was dried over MgSO4 and evaporated. The residue was triturated in hexane/DEE, and recrystallized from heptane to afford the title compound (30.8 g, 67 %) as a yellow oil. IR (KBr): ν 3441, 2970, 1611 cm−1.

1H NMR (600 MHz, CDCl3): δ 7.31 (t, J = 7.5 Hz, 1H), 7.24 (d, J = 7.5 Hz, 1H), 7.20 (s, 1H), 7.18 (d, J = 7.5 Hz, 1H), 7.17 (d, J = 7.5 Hz, 1H), 7.13 (s, 1H), 5.69 (br, 1H), 3.83 (br, 1H), 3.51 (br, 1H), 3.48 (q, J = 7.0 Hz, 2H), 2.83 (t, J = 7.0 Hz, 2H), 1.54 (br, 6H), 1.14 (br, 6H), 1.14 (s, 9H) ppm. 13C NMR (150 MHz, CDCl3): δ 178.41, 170.85, 139.50, 139.30, 129.13, 128.61, 125.92, 123.59, 117.49, 50.96, 45.92, 23.52, 20.65 ppm. HRMS calcd. for C20H21N2O+ ([M+H]+): 298.0810, found 298.0801.

3-(2-Aminomethyl)-N,N-bis(propan-2-yl)benzamide (8). 12 (12.7 g, 52.0 mmol) was hydrogenated in methanolic NH4 solution (250 mL) at 25 °C using H2 at 10 bar and Ra-Ni (4.60 g, ca. 30 % water content, ca. 78 mmol) catalyst for 4 h. After filtration, the solvent was evaporated and the residue was purified by flash chromatography (10–70 % EtOAc in hexane) to afford the title compound (13.7 g, 83 %) as a pale yellow oil. IR (film): ν 3441, 2970, 1611 cm−1.

1H NMR (600 MHz, CDCl3): δ 7.31 (t, J = 7.5 Hz, 1H), 7.24 (d, J = 7.5 Hz, 1H), 7.20 (s, 1H), 7.18 (d, J = 7.5 Hz, 1H), 7.17 (d, J = 7.5 Hz, 1H), 7.13 (s, 1H), 5.69 (br, 1H), 3.82 (br, 1H), 3.51 (br, 1H), 3.48 (q, J = 7.0 Hz, 2H), 2.82 (t, J = 7.0 Hz, 2H), 1.53 (br, 6H), 1.13 (br, 6H) ppm. 13C NMR (150 MHz, CDCl3): δ 171.22, 139.48, 138.75, 129.27, 128.73, 126.16, 123.45, 50.94, 45.85, 42.43, 37.85, 20.65 ppm. HSQC (145 Hz): 7.33−(171.22, 139.48, 138.75, 129.27, 128.73, 126.16, 123.45, 50.94, 45.85, 42.43, 37.85), 20.65 ppm. HRMS calcd. for C19H21N2O2+ ([M+H]+): 286.1411, found 286.1401.

3-[2-(2,2-Dimethylpropanamido)ethyl]-N,N-bis(propan-2-yl)benzamide (13). A solution of BuLi (1.6 M in hexane, 5.6 mL, 9.0 mmol) was added to a solution of 4d (1.00 g, 3.00 mmol) in THF (15 mL) at −78 °C. After stirring for 2 h at −78 °C, DMF (1.40 mL, 1.30 g, 18.1 mmol) was added. The mixture was stirred for 2 h. After warming to ambient temperature, the reaction mixture was diluted with a saturated aqueous solution of NH4Cl (10 mL) and extracted with EtOAc (6 and 2×4 mL). The combined organic layer was dried over MgSO4 and evaporated. The residue was triturated in hexane/DEE, and filtered to afford the title compound (159 mg, 15 %) as a colorless solid. Mp 99−101 °C (hexane/DEE). IR (KBr): v 3431, 1690, 1625 cm−1. 1H NMR (400 MHz, CDCl3): δ 10.05 (br s, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.32 (dd, J = 8.0 Hz, J = 1.6 Hz, 1H), 7.10 (d, J = 1.6 Hz, 1H), 5.72 (br t, J = 6.5 Hz, 1H), 3.57 (m, 1H), 3.55 (m, 1H), 3.50 (br, 2H), 2.91 (t, J = 7.0 Hz, 2H), 1.60 (br, 6H), 1.16 (s, 9H), 1.10 (br d, J = 6.5 Hz, 6H) ppm. 13C NMR (150 MHz, CDCl3): δ 190.14, 178.64, 130.38, 129.32, 128.11, 125.29, 117.49, 50.96, 45.92, 23.52, 20.65 ppm. HRMS calcd. for C20H21N2O2+ ([M+H]+): 333.2537 found 333.2539.

5-[2-(2,2-Dimethylpropanamido)ethyl]-2-formyl-N,N-bis(propan-2-yl)benzamide (14). Period. Polytech. Chem. Eng., 63(4), pp. 629–635, 2019
168.20, 146.53, 141.48, 130.76, 130.05, 129.27, 126.32, 51.25, 46.16, 40.28, 38.68, 35.78, 27.52, 20.53 (br), 20.14 (br) ppm. HSQC: 10.05−(130.76, 130.05), 7.87−129.27, 7.10−126.32, 3.57−51.25, 3.55−46.16, 3.50−40.28, 2.91−35.78, 1.60−20.14, 1.16−27.52, 1.10−20.53, HMBC (7 Hz, characteristic cross-peaks): 10.05−(130.76, 130.05), 7.87−129.27, 126.32, 40.28, 1.16−(178.64, 38.68, 27.52). Selective NOESY: 7.32−35.78, 7.10−35.78, 3.55−168.20, 2.91−(146.53, 129.27, 126.32, 40.28), 1.16−(178.64, 38.68, 27.52).

**References**

[1] Brogden, R. N., Heel, R. C., Speight, T. M., Avery, G. S. "Nominensine: a review of its pharmacological properties and therapeutic efficacy in depressive illness", Drugs, 18(1), pp. 1–24, 1979. [https://doi.org/10.2165/00003495-197918010-00001](https://doi.org/10.2165/00003495-197918010-00001)

[2] Ogijama, T., Yonezawa, K., Inoue, M., Katayama, N., Watanabe, T., Yoshimura, S., Gotoh, T., Kiso, T., Koakatsu, A., Kakimoto, S., Shishikura, J.-I. "Discovery of an 8-methoxytetrahydroisoquinoline derivative as an orally active N-type calcium channel blocker for neuropathic pain without CYP inhibition liability", Bioorganic & Medicinal Chemistry, 23(15), pp. 4638–4648, 2015. [https://doi.org/10.1016/j.bmc.2015.05.053](https://doi.org/10.1016/j.bmc.2015.05.053)

[3] Hargitai, Cs., Nagy, T., Halász, J., Simig, Gy., Volk, B. "Synthesis of 8-fluoro-3,4-dihydroisoquinoline and its transformation to 1,8-disubstituted tetrahydroisoquinolines", Molecules, 23(6), pp. 1280–1290, 2018. [https://doi.org/10.3390/molecules23061280](https://doi.org/10.3390/molecules23061280)

[4] Hargitai, Cs., Nagy, T., Halász, J., Kováiny-Lax, Gy., Németh, G., Simig, Gy., Volk, B. "Synthesis and further transformations of 8-chloro-3,4-dihydroisoquinoline", Tetrahedron, 74(49), pp. 7009–7017, 2018. [https://doi.org/10.1016/j.tet.2018.10.016](https://doi.org/10.1016/j.tet.2018.10.016)

[5] Schlosser, M., Simig, Gy. "8-Methoxyisoquinoline derivatives through ortho-selective metalation of 2-(3-methoxyphenyl)ethylamine", Tetrahedron Letters, 32(17), pp. 1963–1966, 1991. [https://doi.org/10.1016/0040-4039(91)80404-V](https://doi.org/10.1016/0040-4039(91)80404-V)

[6] Lukács, Gy., Pores-Makkay, M., Simig, Gy. "Lithiation of 2-aryl-2-(chloroaryl)-1,3-dioxolanes and its application in the synthesis of new ortho-functionalized benzophenone derivatives", European Journal of Organic Chemistry, 2001(9), pp. 1728−1735, 2001. [https://doi.org/10.1002/ejoc.200000335](https://doi.org/10.1002/ejoc.200000335)

[7] Molnár, B., Németh, A., Kupai, J., Lukács, Gy., Pores-Makkay, M., Kupai, J., Lukács, Gy., Simig, Gy., Volk, B. "Lithiation of 2-aryl-2-methyl-1,3-dioxolanes with PMDTA-complexed butyllithium", Tetrahedron, 73(4), pp. 298–306, 2017. [https://doi.org/10.1016/j.tet.2016.11.072](https://doi.org/10.1016/j.tet.2016.11.072)
[9] Mills, R. J., Taylor, N. J., Snieckus, V. "Directed ortho metalation of N,N-diethylbenzamides. Silicon protection of ortho sites and the α-methyl group", The Journal of Organic Chemistry, 54(18), pp. 4372–4385, 1989. https://doi.org/10.1021/jo00279a028

[10] Sanz, R., Castroviejo, M. P., Guilarte, V., Perez, A., Fananas, F. J. "Regioselective synthesis of 4- and 7-alkoxyindoles from 2,3-dihalophenols: application to the preparation of indole inhibitors of phospholipase A₂", The Journal of Organic Chemistry, 72(14), pp. 5113–5118, 2007. https://doi.org/10.1021/jo070643y

[11] Wang, L., Wang, Y., Guo, F., Zheng, Y., Bhadury, P. S., Sun, Z. "Regioselective formylation of 1,3-disubstituted benzenes through in situ lithiation", Tetrahedron Letters, 54(45), pp. 6053–6056, 2013. https://doi.org/10.1016/j.tetlet.2013.08.098

[12] Mortier, J., Moyroud, J., Benneteau, B., Cain, P. A. "The carboxylic acid group as an effective director of ortho-lithiation", The Journal of Organic Chemistry, 59(15), pp. 4042–4044, 1994. https://doi.org/10.1021/jo00094a007

[13] Gschwend, H. W., Rodriguez, H. R. "Heteroatom-Facilitated Lithiations", In: Denmark, S. E. (ed.) Organic Reactions, John Wiley & Sons, Inc., Hoboken, NJ, USA, 2003, pp. 1–360. https://doi.org/10.1002/0471264180.or026.01

[14] Beak, P., Brown, R. A. "The ortho lithiation of tertiary benzamides", The Journal of Organic Chemistry, 42(10), pp. 1823–1824, 1977. https://doi.org/10.1021/jo00430a042

[15] Snieckus, V. "Directed ortho metalation. Tertiary amide and O-carbamate directors in synthetic strategies for polysubstituted aromatics", Chemical Reviews, 90(6), 879–933, 1990. https://doi.org/10.1021/cr00104a001

[16] Beak, P., Brown, R. A. "The tertiary amide as an effective director of ortho lithiation", The Journal of Organic Chemistry, 47(1), pp. 34–46, 1982. https://doi.org/10.1021/jo00340a008

[17] Faigl, F., Thurner, A., Molnár, B., Simig, Gy., Volk, B. "Manufacturing synthesis of 5-substituted phthalides", Organic Process Research & Development, 14(3), pp. 617–622, 2010. https://doi.org/10.1021/op100049t

[18] Yang, G., Zhang, W. "Regioselective Pd-catalyzed aerobic aza-wacker cyclization for preparation of isindolinones and isoquinolin-1(2H)-ones", Organic Letters, 14(1), pp. 268–272, 2012. https://doi.org/10.1021/ol203043h