



Regioselective synthesis of functionalized 4-nitro- and 4-amino-phenols based on formal [3+3] cyclocondensations of 3-ethoxy-2-nitro-2-en-1-ones with 1,3-bis(silyloxy)-1,3-butadienes

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ABSTRACT

Functionalized 4-nitro- and 4-aminophenols were regioselectively prepared based on [3+3] cyclizations of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with 3-ethoxy-2-nitro-2-en-1-ones.

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Functionalized 4-nitro- and 4-aminophenols are of considerable pharmacological relevance and occur in several natural products.¹ 4-Nitrophenols show antiandrogenetic,^{2a} vasodilative,^{2b} and estrogenic activities.^{2c} A wide range of pharmacological activities have been reported for functionalized 4-aminophenols and related molecules.^{3–8} The synthesis of 4-nitrophenols by nitration of phenols suffers from the low *o/p*-regioselectivity. In addition, several side-reactions are possible for functionalized substrates, due to the harsh reaction conditions. Hydroxy- and nitro-substituted biaryls have been prepared by Ullmann-type reactions, by nucleophilic aromatic substitutions⁹ and by nitration of appropriate biphenyls.¹⁰ However, the scope of these reactions is limited by the harsh reaction conditions and by steric effects. The synthesis of 4-aminophenols and amino-substituted biaryls by palladium(0)-catalyzed coupling reactions¹¹ suffers from the fact that electron-rich arenes, in particular sterically encumbered substrates, sometimes react sluggishly or not at all. Last but not the least, the synthesis of the required starting materials, highly functionalized or sterically encumbered 4-bromo- or 4-iodophenols or 4-bromo- or 4-iodoanilines, can be a difficult and tedious task.

Our strategy to circumvent these problems is based on the application of a 'building block strategy'. Ashburn and co-workers reported the synthesis of 2-nitro-2'-alkoxycarbonyl-biphenyls

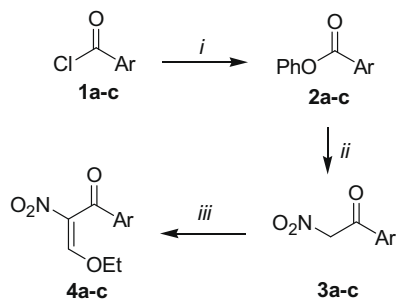
based on [4+2] cycloadditions.¹² Chan and Brownbridge were the first to report¹³ the synthesis of salicylates by formal [3+3] cyclizations of 1,3-bis(silyloxy)-1,3-butadienes¹⁴ with 3-silyloxy-2-en-1-ones. This reaction has been extensively studied in recent years.¹⁵ Herein, we report, for the first time, a convenient synthesis of 4-nitro- and 4-aminophenols based on formal [3+3] cyclizations of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with 3-ethoxy-2-nitro-2-en-1-ones. The products reported herein are not readily available by other methods.

Aryl phenolates **2a–c** were prepared from aryl chlorides **1a–c** according to the literature.¹⁶ The reaction of **2a–c** with nitromethane, following a known procedure,¹⁷ gave the α -nitroacetophenones **3a–c** (Scheme 1, Table 1). The reaction of the latter with triethyl orthoformate and acetic anhydride afforded the 3-ethoxy-2-nitro-2-en-1-ones **4a–c**. 1,3-Bis(silyloxy)-1,3-butadienes **5a–e** were prepared as previously reported.¹³ The TiCl₄-mediated cyclization of **4a** with **5a** afforded the 4-nitrophenol **6a** with excellent regioselectivity (Scheme 2). The best yield was obtained when the reaction was carried out in a highly concentrated solution.¹⁸

The formation of **6a** can be explained by reaction of **4a** with TiCl₄ to give allylic cation **A**. The attack of the terminal carbon atom of **5a** onto **A** resulted in the formation of intermediate **B** (Scheme 2). The elimination of (methoxy)trimethylsilane (intermediate **C**) and subsequent cyclization gave intermediate **D**. The elimination of titanium hydroxide and aromatization resulted in the formation of product **6a**.

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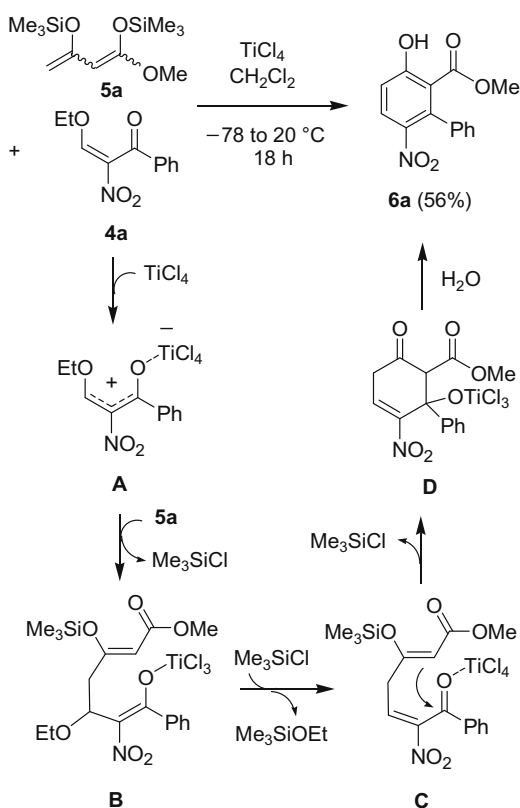


Scheme 1. Synthesis of **4a–c**: (i) PhOH (1.0 equiv), **1a–c** (1.03 equiv), 60 °C; (ii) CH₃NO₂ (1.0 equiv), **2a–c** (0.33 equiv), KOtBu (1.0 equiv), DMSO, 12 h, 0–10 °C; (iii) **3a–c** (1.0 equiv), Ac₂O (1.0 equiv), HC(OEt)₃ (1.2 equiv), 120 °C, 6 h.

Table 1
Synthesis of **6a–i** and **7a–i**

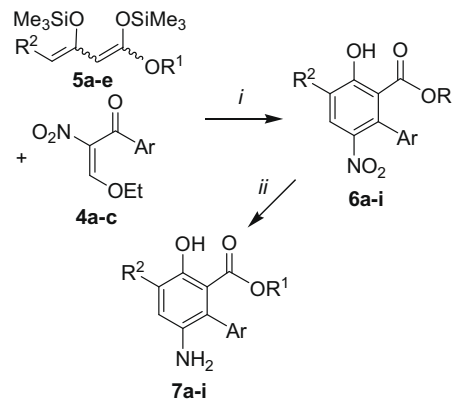
4	5	6,7	Ar	R ¹	R ²	% ^a (6)	% ^a (7)
a	a	a	Ph	Me	H	56	86
a	b	b	Ph	Me	Me	57	85
a	c	c	Ph	Et	Et	65	95
a	d	d	Ph	Me	nBu	58	92
a	e	e	Ph	Me	nOct	62	90
b	a	f	2-MeC ₆ H ₄	Me	H	68	91
b	b	g	2-MeC ₆ H ₄	Me	Me	72	89
c	a	h	2-ClC ₆ H ₄	Me	H	56	88
c	b	i	2-ClC ₆ H ₄	Me	Me	70	90

^a Yields of isolated products.



Scheme 2. Possible mechanism of the formation of **6a**.

The TiCl₄-mediated cyclization of 3-ethoxy-2-nitro-2-en-1-ones **4a–c** with 1,3-bis(trimethylsilyloxy)-1,3-butadienes **5a–e** afforded the 4-nitrophenols **6a–i** in 56–72% yield (Scheme 3, Table 1).



Scheme 3. Synthesis of **6a–i** and **7a–i**: (i) TiCl₄, CH₂Cl₂, –78 → 20 °C, 18 h, (ii) H₂, Pd/C (10 mol %), 20 °C, 48 h.

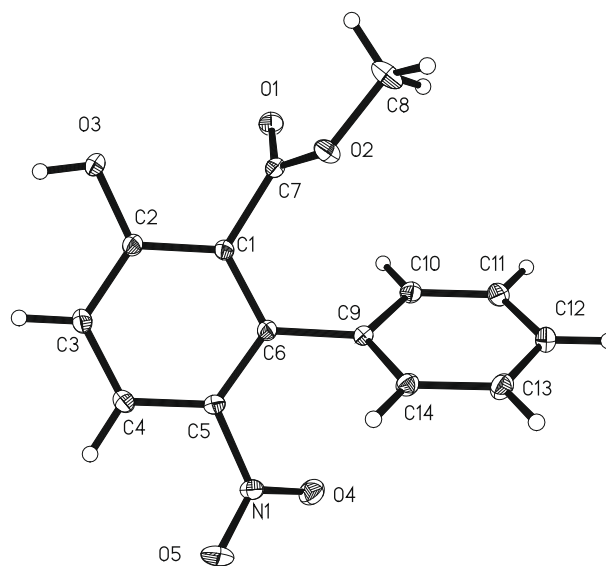


Figure 1. Crystal structure of **6a** (50% probability level).

The yields of the products derived from dienes **5b–e**, containing a substituent located at carbon atom C-4, were higher than those derived from **5a**. The hydrogenation of 4-nitrophenols **6a–i**, in the presence of catalytic amounts of Pd/C (10 mol %), afforded 4-aminophenols **7a–i** in excellent yields (Scheme 3, Table 1).¹⁹

The structures of all compounds were established by spectroscopic methods. The structure of **6a** was independently confirmed by X-ray crystal structure analysis (Fig. 1).²⁰

In conclusion, we have reported the regioselective synthesis of functionalized 4-nitro- and 4-aminophenols based on [3+3] cyclocondensation of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with 3-ethoxy-2-nitro-2-en-1-ones.

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References and notes

- Römpf Lexikon Naturstoffe; Steglich, W., Fugmann, B., Lang-Fugmann, S., Eds.; Thieme: Stuttgart, 1997.
- (a) Li, C.; Taneda, S.; Suzuki, A. K.; Furuta, C.; Watanabe, G.; Taya, K. *Eur. J. Pharmacol.* **2006**, 543, 194; (b) Yoki, K.; Kamata, K.; Toda, N.; Hayashi, H.

- Seki, K.-i.; Taneda, S.; Yoshino, S.; Sakushima, A.; Sakata, M.; Suzuki, A. *K. Biol. Pharm. Bull.* **2003**, 26, 394; (c) Bitsch, N.; Dudas, C.; Koerner, W.; Failing, K.; Biselli, S.; Rimkus, G.; Brunn, H. *Arch. Environ. Contam. Toxicol.* **2002**, 43, 257; (d) Api, A. M.; Gudi, R. *Mutat. Res.* **2000**, 464, 263; (e) Lehman-McKeeman, L. D.; Caudill, D.; Vassallo, J. D.; Pearce, R. E.; Madan, A.; Parkinson, A. *Toxicol. Lett.* **1999**, 111, 105.
3. (a) Nadin, L.; Murray, M. *Biochem. Pharmacol.* **1999**, 58, 1201; (b) Fent, K.; Escher, C.; Caminada, D. *Reprod. Toxicol.* **2006**, 22, 175; (c) Khamdang, S.; Takeda, M.; Noshiro, R.; Narikawa, S.; Enomoto, A.; Anzai, N.; Piyachaturawat, P.; Endou, H. *J. Pharmacol. Exp. Ther.* **2002**, 303, 534; (d) Gobec, S.; Brozic, P.; Rizner, T. L. *Bioorg. Med. Chem. Lett.* **2005**, 15, 5170; (e) Tran, T.; Saheba, E.; Arcerio, A. V.; Chavez, V.; Li, Q.-y.; Martinez, L. E.; Primm, T. P. *Bioorg. Med. Chem.* **2004**, 12, 4809.
4. (a) Alvi, K. A.; Nair, B.; Gallo, C.; Baker, D. J. *Antibiot.* **1997**, 50, 264; (b) de Oliveira, M. F.; Oliveira, J. H. H. L.; Galetti, F. C. S.; de Souza, A. O.; Silva, C. L.; Hajdu, E.; Peixinho, S.; Berlinck, R. G. S. *Planta Med.* **2006**, 72, 437; (c) Lee, J.; Chubb, A. J.; Moman, E.; McLoughlin, B. M.; Sharkey, C. T.; Kelly, J. G.; Nolan, K. B.; Devocelle, M.; Fitzgerald, D. J. *Org. Biomol. Chem.* **2005**, 3, 3678.
5. Alvi, K. A.; Diaz, M. C.; Crews, P.; Slate, D. L.; Lee, R. H.; Moretti, R. J. *Org. Chem.* **1992**, 57, 6604.
6. Ismail, L. D.; Lorenz, P.; Stermitz, F. J. *Nat. Prod.* **1998**, 61, 1174.
7. (a) Davies, J.; Wang, H.; Taylor, T.; Warabi, K.; Huang, X.-H.; Andersen, R. J. *Org. Lett.* **2005**, 7, 5233; (b) Thale, Z.; Johnson, T.; Tenney, K.; Wenzel, P. J.; Lobkovsky, E.; Clardy, J.; Media, J.; Pietraszkiewicz, H.; Valeriote, F. A.; Crews, P. *J. Org. Chem.* **2002**, 67, 9384.
8. (a) Werbel, L. M.; Cook, P. D.; Elslager, E. F.; Hung, J. H.; Johnson, J. L. *J. Med. Chem.* **1986**, 29, 924; (b) Take, K.; Okumura, K.; Takimoto, K.; Kato, M.; Ohtsuka, M.; Shiokawa, Y. *Chem. Pharm. Bull.* **1991**, 39, 2915; (c) Astles, P. C.; Brown, T. J.; Cox, P.; Halley, F.; Lockey, P. M. *Bioorg. Med. Chem. Lett.* **1997**, 7, 907; (d) Ukita, T.; Nakamura, Y.; Kubo, A.; Yamamoto, Y.; Takahashi, M. *J. Med. Chem.* **1999**, 42, 1293; (e) Sun, L.; Tran, N.; Liang, C.; Tang, F.; Rice, A.; Schreck, R.; Waltz, K.; Shawver, L. K.; McMahon, G.; Tang, C. J. *Med. Chem.* **1999**, 42, 5120; (f) Poupart, M.-A.; Cameron, D. R.; Chabot, C.; Ghiro, E.; Goudreau, N.; Goulet, S.; Poirier, M.; Tsantrizos, Y. S. *J. Org. Chem.* **2001**, 66, 4743; (g) Parikh, V.; Welch, W. M.; Schmidt, A. W. *Bioorg. Med. Chem. Lett.* **2003**, 13, 269; (h) Wang, L.; Wang, G. T.; Wang, X.; Tong, Y.; Sullivan, G.; Park, D.; Leonard, N. M.; Li, Q.; Cohen, J.; Gu, W.-Z.; Zhang, H. *J. Med. Chem.* **2004**, 47, 612; (i) Sheppard, G. S.; Kawai, M.; Craig, R. A.; Davidson, D. J.; Majest, S. M.; Bell, R. L.; Henkin, J. *Bioorg. Med. Chem. Lett.* **2004**, 14, 965; (j) Mor, M.; Rivara, S.; Lodola, A.; Plazzi, P. V.; Tarzia, G.; Duranti, A.; Tontini, A.; Piersanti, G.; Kathuria, S.; Piomelli, D. *J. Med. Chem.* **2004**, 47, 4998; (k) Hayakawa, I.; Shioya, R.; Agatsuma, T.; Furukawa, H.; Naruto, S.; Sugano, Y. *Bioorg. Med. Chem. Lett.* **2004**, 14, 4383.
9. (a) Poesche, W. H. *J. Chem. Soc. C* **1966**, 890; (b) Forrest, J. J. *Chem. Soc.* **1960**, 589; (c) Helmchen, G.; Prelog, V. *Helv. Chim. Acta* **1972**, 55, 2599; (d) Suzuki, H.; Enya, T.; Hisamatsu, Y. *Synthesis* **1997**, 1273; (e) Bell, A. J.; Read, R. W. *Aust. J. Chem.* **1987**, 40, 1813.
10. (a) Kleppinger, R.; Lilly, C. P.; Yang, C. J. *Am. Chem. Soc.* **1997**, 119, 4097; (b) Mohanakrishnan, A. K.; Srinivasan, P. C. *J. Org. Chem.* **1995**, 60, 1939.
11. *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004.
12. Ashburn, B. O.; Carter, R. G.; Zakharov, L. N. *J. Am. Chem. Soc.* **2007**, 129, 9109.
13. Chan, T.-H.; Brownbridge, P. J. *Am. Chem. Soc.* **1980**, 102, 3534.
14. For a review of 1,3-bis(silyloxy)-1,3-butadienes, see: Langer, P. *Synthesis* **2002**, 441.
15. Review: Feist, H.; Langer, P. *Synthesis* **2007**, 327.
16. Nakamatsu, S.; Yoshizawa, K.; Toyota, S.; Toda, F.; Matijasic, I. *Org. Biomol. Chem.* **2003**, 1, 13.
17. Field, G. F.; Zally, S. *Synthesis* **1979**, 295.
18. General procedure for the synthesis of 4-nitrophenols **6a–i**: To a CH₂Cl₂ solution (2 mL/1 mmol of **4a–c**) of **4a–c** were added **5a–e** (1.1 mmol) and, subsequently, TiCl₄ (1.1 mmol) at 78 °C. The temperature of the solution was allowed to warm to 20 °C during 18 h with stirring. To the solution was added hydrochloric acid (10%, 20 mL) and the organic and the aqueous layer were separated. The latter was extracted with CH₂Cl₂ (3 × 20 mL). The combined organic layers were dried (Na₂SO₄), filtered, and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, *n*-heptane / EtOAc) to give **6a–i**. Methyl 3-hydroxy-6-nitrobiphenyl-2-carboxylate (**6a**): Reaction starting with **4a** (331 mg, 1.5 mmol) and **5a** (429 mg, 1.7 mmol), **6a** was isolated after chromatography (silica gel, heptanes/EtOAc) as a yellowish solid (230 mg, 56%), mp = 137/138 °C. ¹H NMR (300 MHz, CDCl₃): δ 3.35 (s, 3 H, OCH₃), 7.02 (d, ³J = 9.0 Hz, 1 H, CH_{Ar}), 7.07–7.10 (m, 2 H, CH_{Ph}), 7.27–7.31 (m, 3 H, CH_{Ph}), 7.82 (d, ³J = 8.9 Hz, 1 H, CH_{Ar}), 11.07 (s, 1 H, OH). ¹³C NMR (CDCl₃, 75 MHz): δ = 52.5 (OCH₃), 113.6 (CCOCH₃), 117.7, 127.7, 127.7, 127.7, 127.8, 127.8, 128.5 (CH_{Ar}), 133.7, 136.2, 139.0 (C_{Ar}), 163.8 (COH), 170.2 (CO). IR (KBr, cm⁻¹): ν = 3086 (w), 3062 (w), 2954 (w), 1735 (w), 1670 (m), 1599 (w), 1576 (w), 1525 (m), 1501 (w), 1442 (m), 1324 (m), 1220 (m), 1156 (w), 1132 (m), 1095 (w), 1074 (w), 1026 (w), 970 (w), 907 (m), 837 (w), 813 (w), 769 (w), 727 (s), 698 (m), 672 (m), 648 (w), 584 (w), 553. GC–MS (EI, 70 eV): *m/z* (%) = 273 ([M]⁺, 80), 242 (17), 241 (100), 224 (15), 213 (25), 212 (13), 196 (14), 185 (18), 184 (11), 183 (13), 159 (16), 157 (11), 155 (20), 140 (15), 139 (66), 138 (10), 129 (25), 128 (14), 127 (19), 115 (10), 113 (10), 102 (10), 77 (12), 63 (11). HRMS (EI): calcd for C₁₄H₁₁O₅N ([M]⁺): 273.06317; found: 273.063020.
19. General procedure for the synthesis of 4-aminophenols **7a–i**. To a MeOH suspension (25 mL) (EtOH in case of **7c**) of Pd/C (10 mol %) were added **6a–i** (1.0 equiv). The mixture was set under a hydrogen atmosphere. After stirring for 48 h at 20 °C, the reaction mixture was filtered (Celite) and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, heptanes / EtOAc = 2:1). Methyl 6-amino-3-hydroxybiphenyl-2-carboxylate (**7a**): Starting with **6a** (130 mg, 0.475 mmol), **7a** was isolated (99 mg, 86%) by column chromatography (silica gel, heptanes/EtOAc = 30:1 → 20:1) as a yellowish solid, mp = 95–97 °C. ¹H NMR (300 MHz, CDCl₃): δ 3.02 (br, 2 H, NH₂), 3.30 (s, 3 H, OCH₃), 6.82–6.84 (m, 2 H, CH_{Ar}), 7.08–7.11 (m, 2 H, CH_{Ph}), 7.22–7.35 (m, 3 H, CH_{Ph}), 10.07 (br, 1 H, OH). ¹³C NMR (CDCl₃, 75 MHz): δ = 51.6 (OCH₃), 112.5 (CCOCH₃), 117.7, 123.1, 127.0 (CH_{Ar}), 127.5 (C_{Ar}), 128.5 (2 × CH_{Ar}), 128.9 (2 × CH_{Ar}), 136.9, 139.1 (C_{Ar}), 154.7 (COH), 171.3 (CO). IR (KBr, cm⁻¹): ν = 3742 (w), 3060 (w), 2922 (w), 2788 (w), 2671 (w), 1721 (s), 1586 (m), 1488 (m), 1455 (m), 1433 (m), 1348 (m), 1302 (m), 1277 (s), 1239 (m), 1217 (s), 1158 (m), 1110 (m), 1087 (m), 1029 (w), 982 (m), 949 (m), 911 (m), 871 (m), 807 (m), 776 (m), 750 (m), 730 (m), 719 (s), 698 (s), 646 (m), 613 (m), 549 (m). GC–MS (EI, 70 eV): *m/z* (%) = 243 ([M]⁺, 32), 212 (16), 211 (100), 183 (24), 155 (15), 154 (67), 128 (16), 127 (10), 77 (10). HRMS (EI): calcd for C₁₄H₁₃O₃N ([M]⁺): 243.08899; found: 243.089209.
20. CCDC-720054 contains all crystallographic details of this publication and is available free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or can be ordered from the following address: Cambridge Crystallographic Data Centre, 12 Union Road, GB-Cambridge CB21EZ; Fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk.