Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 2939–2942

TETRAHEDRON
LETTERS

Development of a 9-borabicyclo[3.3.1]nonane-mediated solid-phase Suzuki coupling for the preparation of dihydrostilbene analogs

Ron D. Ferguson, Ning Su and Roger A. Smith*

Department of Chemistry Research, Bayer Research Center, 400 Morgan Lane, West Haven, CT 06516, USA

Received 11 December 2002; revised 10 February 2003; accepted 12 February 2003

Abstract—A novel 9-borabicyclo[3.3.1]nonane-mediated solid-phase Suzuki coupling was developed to generate dihydrostilbenes (bibenzyls) and related compounds. Using optimized conditions (20 mol% $PdCl_2$(dppf), 10 equiv. Et_3N, and 10 equiv. olefin/9-BBN, in 9:1 DMF/H_2O, 50°C, 18 h), high conversions to desired products were generally obtained. A small combinatorial library of derivatives was successfully prepared via radiofrequency tagging and directed sorting techniques. © 2003 Elsevier Science Ltd. All rights reserved.

During the last decade, solid-phase organic synthesis methodologies have been pursued and developed to the extent that a staggering variety of synthetic transformations can now be achieved on polymer support.[1] These research efforts have been stimulated in large part by the successful application of solid-phase synthesis for the preparation of small arrays of compounds, and combinatorial libraries, for the discovery and optimization of biologically-active substances.[2] One chemical transformation of key importance in organic synthesis is carbon–carbon bond formation, and it follows that solid-phase synthesis examples of such chemistry have received considerable attention.[3]

As part of one of our medicinal chemistry research programs, we had interest in compounds based on a dihydrostilbene template structure. Indeed, the dihydrostilbene (bibenzyl) fragment has been recognized as an important or 'privileged' substructure in known drugs and protein ligands.[4] Traditional solution-phase methodologies that have been used for the preparation of such derivatives involved palladium-catalyzed coupling of an aryl acetylene to an aryl bromide (Sonogashira coupling), followed by reduction to give the ethylene linker. Although solid-phase examples of this type of coupling step are known,[3,5] reduction of the alkene on solid-phase was not precedented and was considered to be a substantial challenge. The Suzuki coupling reaction mediated by 9-BBN (9-borabicyclo[3.3.1]nonane),[6] which would lead directly to the desired ethylene linker fragment, was considered as a viable alternative route to dihydrostilbenes. In their elegant solid-phase synthesis of prostaglandins, Ellman and co-workers achieved Suzuki cross-coupling of alkyl-9-BBN derivatives with vinyl bromides.[7] A more recent article by Jackson and colleagues describes cross-couplings by hydroboration of a Wang resin-supported alkyl olefin, followed by transmetallation with diethyl zinc, and subsequent palladium-catalyzed coupling with aryl iodides.[8] In this article, we describe our development and application of a 9-borabicyclo[3.3.1]nonane-mediated solid-phase Suzuki coupling to generate dihydrostilbenes and related compounds.

In our exploratory methodology studies, *N*-Fmoc-phenylalanine was coupled to Wang resin, *N*-deprotected by treatment with piperidine, and then coupled with *p*-bromophenyl carbonyl or sulfonyl chloride. The two bromide substrates were then treated with the adduct obtained from 9-BBN and styrene, using a wide variety of reaction conditions for the Suzuki cross-coupling. Reactions were carried out on 10 µmol scale, using 20 mol% $Pd(PPh_3)_4$ or dichloro bis(diphenylphosphino)ferrocenyl palladium [$PdCl_2$(dppf)] as catalyst; NaOH, NaOMe, K_2CO_3, K_3PO_4, $CsCO_3$, or Et_3N as base (5–10 equiv.); and THF, aq. THF, DMF, or aq. DMF as solvent.[9] The reaction mixtures were heated at 50°C for 18 h, and then, following cleavage from the resin, the conversion to desired product was assessed by LC–MS analysis.[9]

---

* Corresponding author. Tel.: +1-203-812-2154; fax: +1-203-812-6182; e-mail: roger.smith.b@bayer.com

0040-4039/03/$ - see front matter
doi:10.1016/S0040-4039(03)00415-5

Overall, this set of trial reactions demonstrated that the dihydrostilbene product could be obtained in good yield, and that the preferred catalyst was $PdCl_2$(dppf), with NaOH, K_2CO_3, and Et_3N identified as the preferred bases.

In a second trial, the preferred reaction conditions were assessed for four additional 9-BBN/aryl olefin adducts. From these experiments, it was concluded that the most consistent and best results were obtained by using 20 mol% $PdCl_2$(dppf), 10 equiv. Et_3N, and 10 equiv. olefin/9-BBN, in 9:1 DMF/H_2O, 50°C, 18 h. High conversion to the desired product was observed in most cases. Unfortunately, in the case of 2,4,6-trimethylstyrene, no detectable amount of product was formed, presumably due to suppressed formation of the 9-BBN adduct intermediate resulting from steric hindrance by the two *ortho* methyl groups.

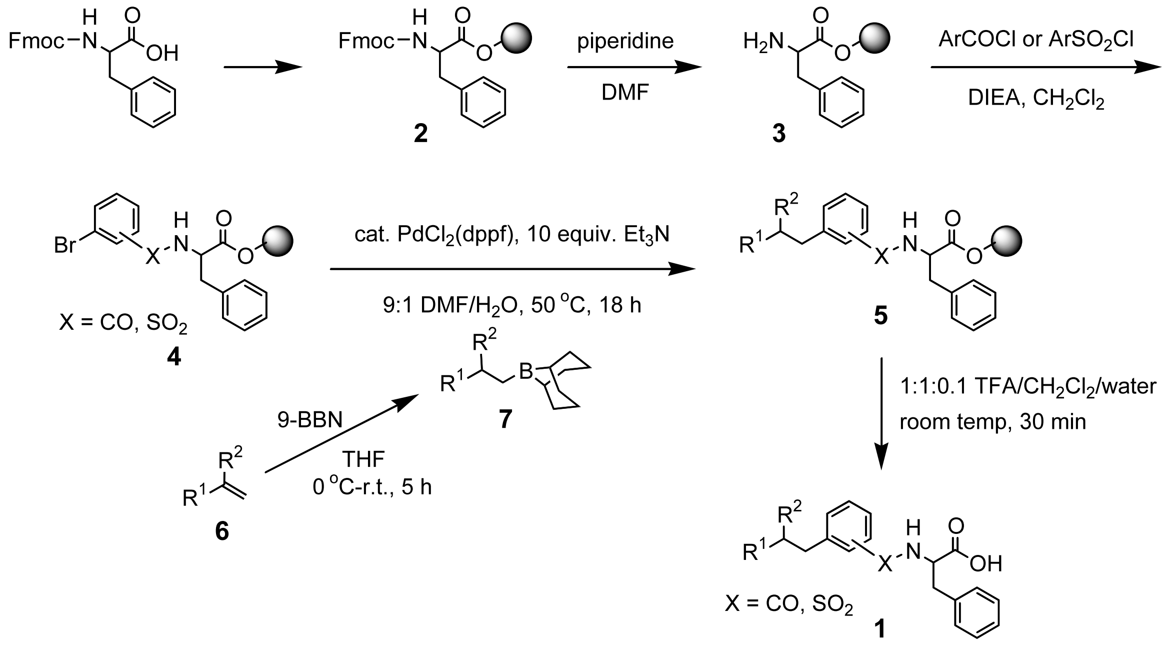
The optimized methodology was then applied to a prototype combinatorial synthesis, on 40 μmol scale and using IRORI MicroKans (microreactors).[10] Thus, Fmoc-phenylalanyl Wang resin was prepared and deprotected,[11] and then coupled with *m*- and *p*-bromophenyl carbonyl and sulfonyl chlorides (four reactions, 9 MicroKans per reaction).[12] After directed sorting guided by radiofrequency-tag scanning, the intermediates were subjected to the 9-borabicyclo[3.3.1]nonane-mediated Suzuki coupling conditions, using nine olefin substrates (9 reactions, 4 MicroKans per reaction).[13] Reaction products were cleaved from the resin, and analyzed by LC–MS/UV/ELSD. The results are summarized in Table 1. In several cases, the products were purified by preparative reverse phase HPLC, and then characterized by NMR and MS.[14] Yields of these purified products were generally in the range 20–45%, based on the substitution level for the Fmoc-phenylalanyl Wang resin **2**, and the mass of product **1** obtained after HPLC purification.[14] In general, these isolated yields correlated with the percent conversion values determined by HPLC (Table 1).

Several trends are evident from the product analyses listed in Table 1. First, similar results are obtained for

Table 1. Dihydrostilbene (R^1 = aryl) and related analogs **1** prepared by solid-phase synthesis according to Scheme 1

Cpd	X	Isomer	R^1	R^2	Conversion[a] (%)
1a	CO	*para*	Ph	H	>99 (92)
1b	CO	*meta*	Ph	H	97 (83)
1c	SO_2	*para*	Ph	H	>99 (80)
1d	SO_2	*meta*	Ph	H	>99 (69)
1e	CO	*para*	4-MeO-Ph	H	>99 (89)
1f	CO	*meta*	4-MeO-Ph	H	93 (72)
1g	SO_2	*para*	4-MeO-Ph	H	95 (74)
1h	SO_2	*meta*	4-MeO-Ph	H	90 (74)
1i	CO	*para*	2-MeO-Ph	H	<1
1j	CO	*meta*	2-MeO-Ph	H	<1
1k	SO_2	*para*	2-MeO-Ph	H	<1
1l	SO_2	*meta*	2-MeO-Ph	H	<1
1m	CO	*para*	3-NO_2-Ph	H	47 (35)
1n	CO	*meta*	3-NO_2-Ph	H	55 (50)
1o	SO_2	*para*	3-NO_2-Ph	H	66 (71)
1p	SO_2	*meta*	3-NO_2-Ph	H	72 (82)
1q	CO	*para*	4-AcO-Ph	H	97 (85)
1r	CO	*meta*	4-AcO-Ph	H	87 (71)
1s	SO_2	*para*	4-AcO-Ph	H	>99 (86)
1t	SO_2	*meta*	4-AcO-Ph	H	>99 (81)
1u	CO	*para*	Ph	Me	>99 (88)
1v	CO	*meta*	Ph	Me	98 (81)
1w	SO_2	*para*	Ph	Me	>99 (91)
1x	SO_2	*meta*	Ph	Me	>99 (72)
1y	CO	*para*	4-Pyridinyl	H	<1
1z	CO	*meta*	4-Pyridinyl	H	<1
1aa	SO_2	*para*	4-Pyridinyl	H	<1
1bb	SO_2	*meta*	4-Pyridinyl	H	<1
1cc	CO	*para*	2-Quinolinyl	H	22 (28)
1dd	CO	*meta*	2-Quinolinyl	H	18 (34)
1ee	SO_2	*para*	2-Quinolinyl	H	74 (56)
1ff	SO_2	*meta*	2-Quinolinyl	H	20 (42)
1gg	CO	*para*	Cyclohexyl	H	>99 (>99)
1hh	CO	*meta*	Cyclohexyl	H	>99 (92)
1ii	SO_2	*para*	Cyclohexyl	H	>99 (77)
1jj	SO_2	*meta*	Cyclohexyl	H	>99 (63)

[a] Percent conversion based on purity of crude product; analyses by LC–MS/ELSD (and LC–MS/UV at 254 nm). (ELSD: evaporative light-scattering detection.)



Scheme 1. Solid-phase synthesis of dihydrostilbenes (R^1 = aryl) and related analogs **1**.

polymer-supported aryl bromides **4** substituted at either the 3- or 4-position, with either sulfonyl or carbonyl amide groups. Regarding the styrene reagents **6**, both electron-donating and -withdrawing substituents on the phenyl ring are well-tolerated, and high conversions to products **1** are obtained. However, reactions with *ortho*-methoxy styrene failed to provide significant amounts of the desired products (Table 1, **1i**–**1l**). In contrast, a disubstituted olefin, namely 2-phenylpropene (**6**, R^1 = Ph, R^2 = CH_3), gave high conversions to products (Table 1, **1u**–**1x**). Heteroaryl olefins **6** were also investigated; however, results were only fair, with 4-vinylpyridine giving no significant amounts of product, and 2-vinylquinoline giving modest yields (Table 1, **1y**–**1ff**). Finally, the methodology was successfully extended to an alkyl olefin, namely vinylcyclohexane (**6**, R^1 = cyclohexyl, R^2 = H) (Table 1, **1gg**–**1jj**).

In summary, we have developed optimal conditions for a solid-phase 9-BBN-mediated Suzuki coupling, to permit the preparation of a variety of dihydrostilbenes and related derivatives. The application of this methodology was successfully demonstrated by the preparation of a small combinatorial library, using radiofrequency tagging and directed sorting techniques.

Acknowledgements

We wish to thank Anthony Paiva and Lee Huang for LC–MS analyses, and Wendy Lee and William Scott for helpful discussions.

References

1. (a) Wendeborn, S.; De Masmaeker, A.; Brill, W. K.-D.; Berteina, S. *Acc. Chem. Res.* **2000**, *33*, 215; (b) Hall, S. E. *Mol. Diversity* **1999**, *4*, 131; (c) Lebl, M. *Curr. Opin. Drug Discovery Dev.* **1999**, *2*, 385; (d) Booth, S.; Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1998**, *54*, 15385.
2. (a) Dolle, R. E. *J. Comb. Chem.* **2002**, *4*, 369; (b) Dolle, R. E. *J. Comb. Chem.* **2001**, *3*, 477; (c) Dolle, R. E. *J. Comb. Chem.* **2000**, *2*, 383.
3. (a) Franzen, R. *Can. J. Chem.* **2000**, *78*, 957; (b) Kingsbury, C. L.; Mehrman, S. J.; Takacs, J. M. *Curr. Org. Chem.* **1999**, *3*, 497; (c) Lorsbach, B. A.; Kurth, M. J. *Chem. Rev.* **1999**, *99*, 1549.
4. (a) Hajduk, P. J.; Bures, M.; Praestgaard, J.; Fesik, S. W. *J. Med. Chem.* **2000**, *43*, 3443; (b) Bemis, G. W.; Murcko, M. A. *J. Med. Chem.* **1996**, *39*, 2887.
5. Berteina, S.; Wendeborn, S.; Brill, W. K.-D.; De Mesmaeker, A. *Synlett* **1998**, 676.
6. (a) Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314; (b) Collier, P. N.; Campbell, A. D.; Patel, I.; Taylor, R. J. K. *Tetrahedron Lett.* **2000**, *41*, 7115.
7. Thompson, L. A.; Moore, F. L.; Moon, Y.-C.; Ellman, J. A. *J. Org. Chem.* **1998**, *63*, 2066.
8. Jackson, R. F. W.; Oates, L. J.; Block, M. H. *Chem. Commun.* **2000**, 1401.
9. Trial reactions were conducted in 2-mL 96-well polypropylene microtiter plates on 10 µmol scale. The reaction mixtures were sonicated (30 min, rt), and then heated at 50°C for 18 h without mixing. Conversion to the desired product was assessed by LC–MS analysis, following cleavage from resin (1:1:0.1 TFA/CH_2Cl_2/water, 30 min, rt).
10. (a) Nicolaou, K. C.; Xiao, X.-Y.; Parandoosh, Z.; Senyei, A.; Nova, M. P. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2289; (b) Xiao, X.-Y.; Parandoosh, Z.; Nova, M. P. *J. Org. Chem.* **1997**, *62*, 6029; (c) IRORI, 9640 Towne Centre Drive, San Diego, CA 92121, USA.

11. IRORI MicroKans were each loaded with 30 mg Wang-polystyrene resin (Novabiochem, 100–200 mesh, 1.30 mmol/g declared substitution), and then *N*-Fmoc-phenylalanine was loaded onto the resin by using Sieber's 2,6-dichlorobenzoyl chloride coupling method.[15] Resin loading by UV–vis spectroscopy (analysis of released Fmoc-piperidine adduct at $\lambda = 302$ nm, $\varepsilon = 8200$ M^{-1} cm^{-1})[16] was found to be 1.37 mmol/g or 105% of theoretical substitution. Just prior to the reaction with sulfonyl or carbonyl chloride, the resin was *N*-Fmoc-deprotected by treatment with 30% piperidine in DMF (30 min, rt), washed with DMF (5×), MeOH (3×), DCM (3×), and MeOH (3×), and dried in vacuo.
12. Conversion of **3** to **4** was achieved by treatment with 3 molar equiv. of the appropriate carbonyl or sulfonyl chloride, plus diisopropylethylamine (3 equiv.), in dichloromethane with mixing at rt overnight.
13. Each olefin **6** (10 equiv.) was separately treated at 0°C with 9-BBN (11 equiv.) in THF under argon, and then the mixtures were allowed to warm to rt, and were mixed by shaking at rt for 5 h. MicroKans containing **4** were treated with a solution of triethylamine (10 equiv.) and $PdCl_2$(dppf) (0.2 equiv.) in degassed DMF/water (9:1). The olefin/9-BBN reaction mixtures (**7**) were then added under argon, the reaction mixtures were capped, and the mixtures were mixed by orbital shaking at 50°C for 18 h. The mixtures were then cooled to rt, filtered, washed with DMF (7×), MeOH (5×), DCM (3×), MeOH (3×), and DCM (2×), and dried in vacuo. MicroKans were sorted, and then individually treated with 1:1:0.1 TFA/DCM/water at rt for 2 h, to release the products **1**.
14. Proton (^{1}H) nuclear magnetic resonance (NMR) spectra were measured in DMSO-d_6 solution with a General Electric GN-Omega 400 (400 MHz) spectrometer, using residual protonated solvent (DMSO δ 2.49) as reference standard. HPLC-electrospray mass spectra (LC–MS) were obtained using a Finnigan LCQ ion-trap mass spectrometer with electrospray ionization, and a YMC Pro C18 2.0×23 mm column. Gradient elution from 90% A to 95% B over 6 min was used on the HPLC, in which buffer A was 98% water, 2% acetonitrile and 0.02% TFA, and buffer B was 98% acetonitrile, 2% water and 0.02% TFA. Representative examples of isolated products are as follows:

    Compound **1a**, *N*-[4-(2-phenylethyl)benzoyl]phenylalanine (3.5 mg, 23%): ^{1}H NMR δ 12.80 (bs, 1H), 8.60 (d, 2H), 7.65 (m, 2H), 7.10–7.30 (m, 12H), 4.60 (m, 1H), 2.85–3.20 (m, 6H); LC–MS *m*/*z* 374.1 (MH^+), t_R 3.24 min. Calcd exact mass for $C_{24}H_{23}NO_3 = 373.2$.

    Compound **1g**, *N*-({4-[2-(4-methoxyphenyl)ethyl]phenyl}sulfonyl)phenylalanine (0.9 mg, 5%): ^{1}H NMR δ 12.80 (bs, 1H), 7.45 (d, 2H), 7.25 (d, 2H), 7.10–7.20 (m, 8H), 6.80 (d, 2H), 3.70 (s, 3H), 3.65 (m, 1H), 2.70–2.90 (m, 6H); LC–MS *m*/*z* 440.1 (MH^+), t_R 3.26 min. Calcd exact mass for $C_{24}H_{25}NO_5S = 439.2$.

    Compound **1p**, *N*-({3-[2-(3-nitrophenyl)ethyl]phenyl}sulfonyl)phenylalanine (3.9 mg, 21%): ^{1}H NMR δ 12.75 (bs, 1H), 8.20 (d, 1H), 8.10 (t, 1H), 8.00 (m, 1H), 7.65 (m, 1H), 7.55 (m, 1H), 7.45 (m, 1H), 7.30–7.40 (m, 3H), 7.05–7.20 (m, 5H), 3.80 (m, 1H), 2.80–3.00 (m, 5H), 2.65 (m, 1H); LC–MS *m*/*z* 455.0 (MH^+), t_R 3.17 min. Calcd exact mass for $C_{23}H_{22}N_2O_6S = 454.1$.

    Compound **1s**, *N*-[(4-{2-[4-(acetyloxy)phenyl]ethyl}phenyl)sulfonyl]phenylalanine (6.0 mg, 32%): ^{1}H NMR δ 12.75 (bs, 1H), 8.20 (d, 1H), 7.45 (m, 2H), 6.95–7.15 (m, 11H), 3.80 (m, 1H), 2.90 (m, 5H), 2.70 (m, 1H), 2.15 (s, 3H); LC–MS *m*/*z* 468.1 (MH^+), t_R 3.16 min. Calcd exact mass for $C_{25}H_{25}NO_6S = 467.1$.

    Compound **1u**, *N*-[4-(2-phenylpropyl)benzoyl]phenylalanine (6.8 mg, 44%): ^{1}H NMR δ 12.70 (bs, 1H), 8.55 (d, 1H), 7.60 (m, 2H), 7.10–7.30 (m, 12H), 4.55 (m, 1H), 2.80–3.20 (m, 5H), 1.15 (d, 3H); LC–MS *m*/*z* 388.1 (MH^+), t_R 3.34 min. Calcd exact mass for $C_{25}H_{25}NO_3 = 387.2$.

    Compound **1ee**, *N*-({4-[2-(2-quinolinyl)ethyl]phenyl}sulfonyl)phenylalanine (3.9 mg, 21%): ^{1}H NMR δ 12.80 (bs, 1H), 8.40 (d, 1H), 8.20 (d, 1H), 8.00 (m, 2H), 7.80 (t, 1H), 7.60 (t, 1H), 7.55 (d, 1H), 7.40 (m, 2H), 7.30 (m, 2H), 7.00–7.20 (m, 5H), 3.80 (m, 1H), 3.15–3.30 (m, 4H), 2.90 (m, 1H), 2.70 (m, 1H); LC–MS *m*/*z* 461.3 (MH^+), t_R 2.22 min. Calcd exact mass for $C_{26}H_{24}N_2O_4S = 460.2$.

    Compound **1ii**, *N*-{[4-(2-cyclohexylethyl)phenyl]sulfonyl}phenylalanine (5.6 mg, 34%): ^{1}H NMR δ 12.75 (bs, 1H), 8.20 (d, 1H), 7.40 (d, 2H), 7.05–7.20 (m, 7H), 3.80 (m, 1H), 2.90 (m, 1H), 2.65 (m, 3H), 1.70 (m, 5H), 1.45 (m, 2H), 1.20 (m, 4H), 0.90 (m, 2H); LC–MS *m*/*z* 416.1 (MH^+), t_R 3.72 min. Calcd exact mass for $C_{23}H_{29}NO_4S = 415.2$.
15. Sieber, P. *Tetrahedron Lett*. **1987**, *28*, 6147.
16. Bunin, B. A. *The Combinatorial Index*; Academic Press: New York, 1998; p. 219.