Green Chemistry

Cite this: *Green Chem.*, 2011, **13**, 847

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COMMUNICATION

Fluorous benzaldehyde-based synthesis of biaryl-substituted oxazabicyclo[3.3.1]nonanes†

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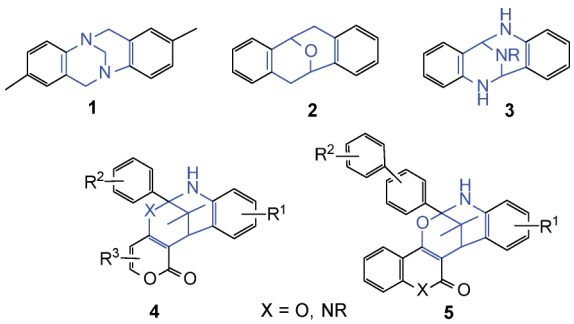
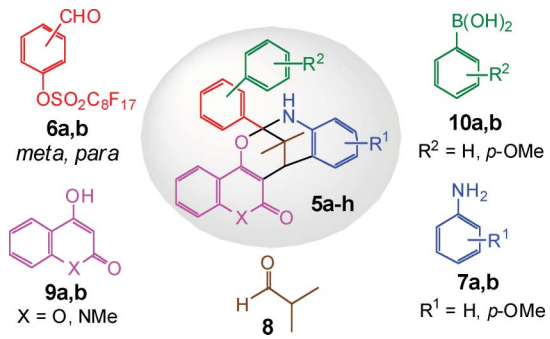
Received 24th October 2010, Accepted 16th February 2011
DOI: 10.1039/c0gc00725k

Fluorous benzaldehyde-based synthesis of biaryl-substituted oxazabicyclo[3.3.1]nonanes is accomplished by a three-step synthesis including multicomponent reaction (MCR) to form tetrahydroquinoline, followed by cycloaddition with coumarin to form oxazabicycles, and then a Suzuki coupling to introduce the biaryl group. Microwave irradiation and fluorous solid-phase extraction (F-SPE) are employed to speed up reactions and simplify product purification.

The cleft-shaped biaryl-fused heterobicyclo[3.3.1]nonanes are a well-studied scaffold in molecular recognition.[1] They have also been investigated as host molecules in enzymatic inhibition[2] and DNA interaction,[3] as well as catalysts for asymmetric synthesis.[4] One of the best known heterobicyclo[3.3.1]nonanes is Troger's base **1** which has a central diazabicycle fused with two benzene rings.[5] Other nitrogen- and oxygen-containing heterobicyclo[3.3.1]nonanes, such as **2** and **3**, have been incorporated in the design of functionalized materials[6] and molecules with biological interest.[7] The Yang group recently reported the utility of diazobicyclo- and oxazobicyclo[3.3.1]nonanes **4** as photochromic colorants.[8] The compound libraries were prepared by a two-step synthesis including a multicomponent reaction (MCR) to form tetrahydroquinoline, followed by a cycloaddition with a 1,3-diketone or an enamine derivative.[8d] Described in this paper is a modified method for the preparation of biaryl-substituted oxazobicyclo[3.3.1]nonanes **5** by using: 1) microwave irradiation to speed up the reactions; 2) fluorous linker to facilitate intermediate purifications and reduce the amount of waste solvent; and 3) Suzuki coupling to remove the fluorous linker and introduce the biaryl-functionality to the bicyclic system. The new method has high synthetic efficiency, provides additional molecular diversity, and also has green chemistry advantages.[9]



As part of our continuous effort in the development of microwave-assisted fluorous synthesis for the preparation of heterocyclic compound libraries,[10] we have demonstrated that perfluorooctanesulfonyl benzaldehydes are a feasible synthon for MCRs to assemble heterocyclic scaffolds.[11] The reaction intermediates can be purified by simple fluorous solid-phase extraction (F-SPE)[12] The fluorous linker can be removed by microwave-promoted coupling reactions to introduce new functional groups.[13] In the current project, the fluorous benzaldehydes **6** were used as a key component to react with four other building blocks **7** to **10** to prepare diaryl-substituted oxazobicyclo[3.3.1]nonanes **5** (Scheme 1).



Scheme 1

We have developed a three-step synthetic sequence for the preparation of diaryl-substituted oxazobicyclo[3.3.1]nonanes **5**. The first step was a three-component reaction of fluorous benzaldehyde **6** with aniline **7** and isobutyraldehyde **8** to form tetrahydroquinoline **11** (Scheme 2).[14] The reactions were catalysed by 0.4 eq. of $Yb(OTf)_3$ under microwave irradiation

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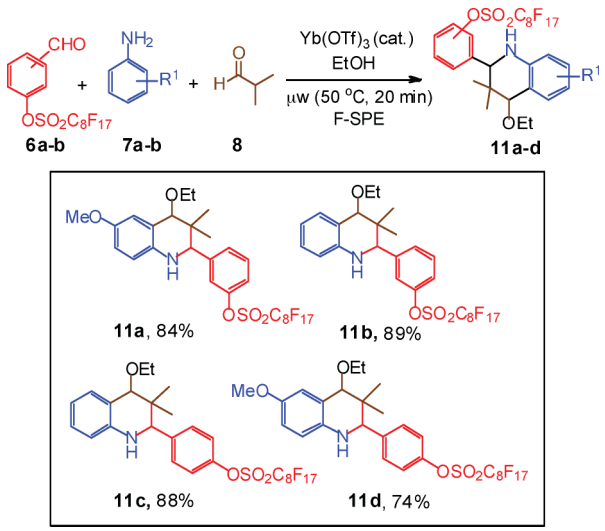
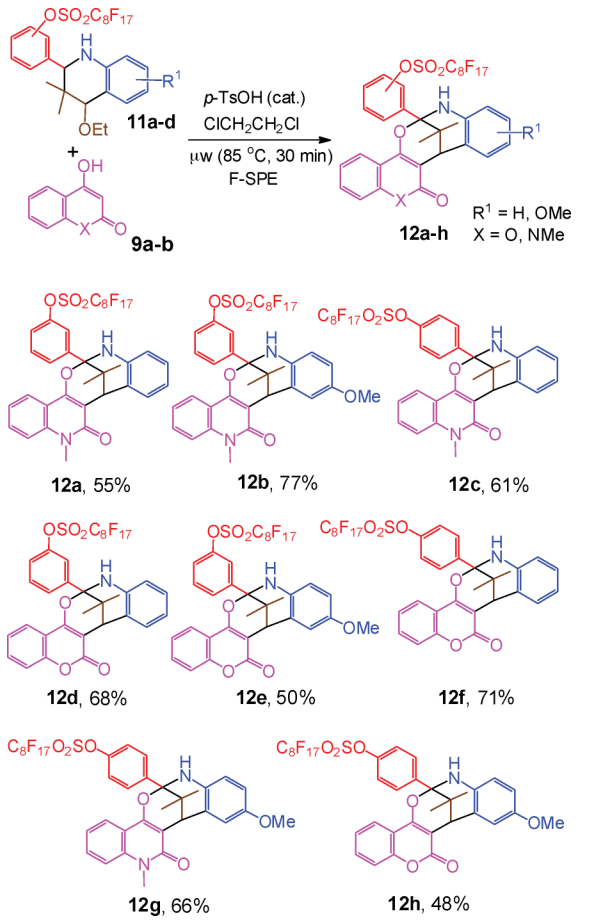
† This publication is part of the web themed issue on fluorine chemistry.



Scheme 2

at 50 °C for 20 min.[15] Fluorous component **6** was used as the limiting agent, while compounds **7** and **8** were used in excess (1.5 eq.) to ensure **6** was consumed. It was interesting to find that under these reaction conditions, the product was the *O*-ethylated ether **11** generated by the reaction of the initial MCR product with solvent ethanol. The reaction mixture was purified by F-SPE, eluted with 80 : 20 MeOH–H_2O and then 100% MeOH.[16]

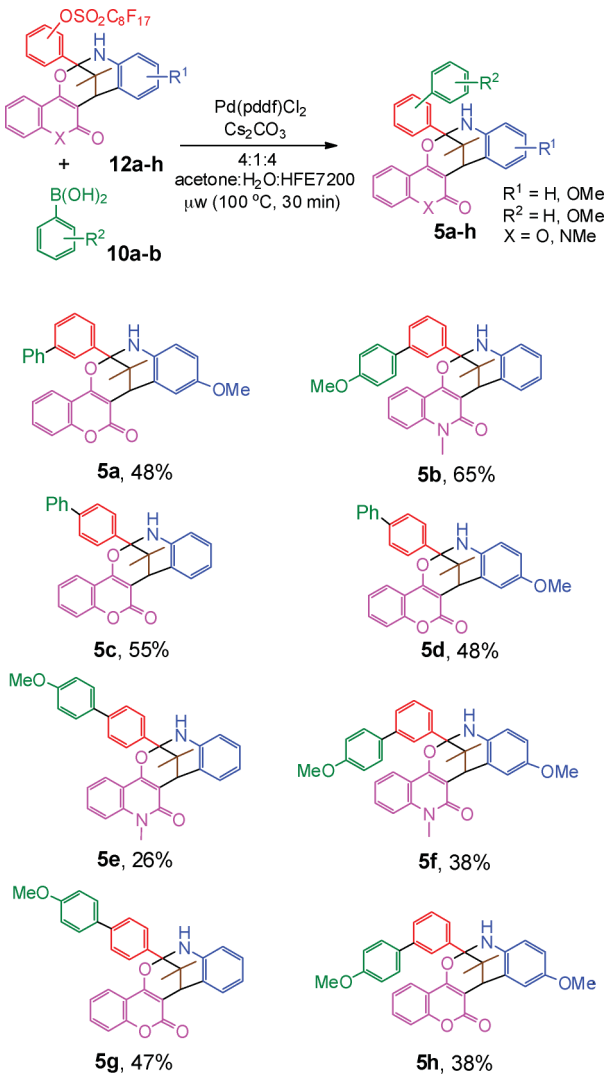


Scheme 3

All the non-fluorous components went into the MeOH–H_2O fraction and compound **11** was collected in the MeOH fraction. Four tetrahydroquinolines **11** were prepared in 74–89% yields.[17]

The cycloaddition of tetrahydroquinoline **11** with coumarin or 4-hydroxy-1-methylquinolin-2(1*H*)-one was carried out under microwave irradiation using 0.2 eq. of *p*-TsOH as a catalyst (Scheme 3). Compound **9** was used in excess (1.5 eq.) to promote the reaction completion. Eight oxazabicycles **12** were prepared in 48–77% yields after F-SPE purification.[18]

The removal of the fluorous linker and introduction of the biaryl functional group to oxazabicycle was accomplished by a microwave-promoted Suzuki coupling reaction (Scheme 4).[19] The aryl perfluorooctanesulfonyl group is a triflate equivalent which can be used for Pd-catalyzed cross-coupling reactions. The reaction was carried out using $Pd(dppf)Cl_2$ as a catalyst, 4 : 1 : 4 acetone : H_2O : HFE7200 ($C_4F_9OC_2H_5$) as a co-solvent, and Cs_2CO_3 as a base under microwave heating at 100 °C for 30 min. Fluorous solvent HFE7200 was used to increase the solubility of the fluorous sample. Eight compounds **5** were prepared in 26–65% yields after F-SPE followed by flash chromatography purification.[20] The structures of the final products



Scheme 4

were characterized by LC-MS, ^{1}H and ^{13}C NMR analyses. The cleaved fluorous linker as $C_8F_{17}SO_2H$ was collected in the MeOH fraction of F-SPE. This compound can be converted to active linkers $C_8F_{17}SO_2F$ or $C_8F_{17}SO_2Cl$ for reuse.[21]

In summary, a fluorous benzaldehyde-based method for the preparation of biaryl-substituted oxazabicyclo[3.3.1]nonanes has been developed. High synthetic efficiency with green chemistry advantages are realized by conducting multicomponent reactions for atom economy, microwave reactions for short reaction times, F-SPE for easy purification of intermediates and reducing the amount of waste solvent, and Suzuki coupling reaction to remove the fluorous linker and introduce the biaryl functional group. This synthetic protocol can be applied to prepare a big compound library by using an expanded number of building blocks.

This work was supported by the University of Massachussetts Boston Healey grant. We thank Weiyi Li, Minh-Thu N. Huynh and Min Lin for particitaing some experimental works of this project.

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17 A representative procedure for the synthesis of compounds **11b**. To a solution of fluorous benzaldehyde **6a** (1.2 g, 2.0 mmol) in ethanol (4 mL) was added aniline **7** (272 μL, 3.0 mmol), isobutyraldehyde **8** (273 μL, 3.0 mmol) and $Yb(OTf)_3$ (496 mg, 0.8 mmol). The mixture was heated under microwave (Biotage Initiator 8) at 50 °C for 20 min. The reaction mixture was purified by F-SPE eluted with 40 mL of 80 : 20 MeOH–H_2O and then 40 mL of MeOH. The, MeOH fraction was concentrated to give **11b** (1.3 g, 89% yield). An analytical sample was obtained by further purification by flash chromatography with 0–20% gradient of EtOAc–hexanes. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.67 (s, 3H), 0.93 (s, 3H), 1.20 (t, J = 13.8 Hz, 3H), 3.44–3.50 (m, 1H), 3.62–3.69 (M, 2H), 4.15 (s, 1H), 4.61 (s, 1H), 6.61–6.71 (m, 2H), 7.10–7.17 (m, 2H), 7.24 (d, J = 8.1 Hz, 1H), 7.40–7.50 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.5, 19.1, 23.4, 36.2, 59.6, 64.4, 83.0, 114.3, 116.6, 119.9, 120.5, 122.0, 129.1, 129.2, 129.6, 131.0, 143.6, 144.1, 149.7. LC-MS (APCI+) m/z 734 $[M + 1]^+$.

18 A representative procedure for the synthesis of compounds **12e**. To a solution of **11a** (469 mg, 0.6 mmol) in 1,2-dichloroethane (3 mL) was added coumarin (146 mg, 0.9 mmol) and *p*-toluenesulfonic acid (21 mg, 0.1 mmol). The mixture was heated under microwave (Biotage Initiator 8) at 85 °C for 30 min. The reaction mixture was purified by F-SPE eluted with 20 mL of 80 : 20 MeOH–H_2O and then 20 mL of MeOH. The, MeOH fraction was concentrated to give **12e** (393 mg, 71% yield). An analytical sample was obtained by further purification by flash chromatography with 0–10% gradient of EtOAc–hexanes. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (s, 3H), 1.02 (s, 3H), 3.78 (s, 3H), 3.84 (s, 1H), 4.99 (s, 1H), 6.57 (d, J = 8.4 Hz, 1H), 6.65 (dd, J = 2.7 Hz, 3.0 Hz, 1H), 7.09 (d, J = 2.4 Hz, 1H), 7.24–7.32 (m, 2H), 7.42 (d, J = 7.8 Hz, 1H), 7.49–7.72 (m, 2H), 7.79 (s, 1H), 7.81 (d, J = 4.8 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.2, 22.9, 33.4, 42.1, 55.9, 96.0, 106.1, 113.8, 114.3, 115.5, 116.9, 122.1, 122.4, 122.7, 124.1, 125.6, 128.8, 129.9, 131.9, 132.6, 141.5, 149.7, 152.4, 153.5. LC-MS (APCI+) m/z 924 $[M + 1]^+$.

19 W. Zhang, C. H.-T. Chen, Y. Lu and T. Nagashima, *Org. Lett.*, 2004, **6**, 1473–1476. See also ref. 11a.

20 A representative procedure for the synthesis of compounds **5d**. To a solution of **12h** (92 mg, 0.1 mmol) in a co-solvent of 4 : 1 : 4 acetone: H_2O: HFE 7200 (3 mL) was added phenylboronic acid **10a** (18 mg, 0.15 mmol), Cs_2CO_3 (81 mg, 0.25 mmol) and $Pd(dppf)Cl_2$ (16 mg, 0.02 mmol). The mixture was heated under microwave (Biotage Initiator 8) at 100 °C for 30 min. The reaction mixture was purified by flash chromatography with 0–30% gradient of EtOAc–hexanes to give **5d** (24 mg, 48% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02 (s, 3H), 1.05 (s, 3H), 3.78 (s, 3H), 3.85 (s, 1H), 5.05 (s, 1H), 6.56 (d, J = 8.7 Hz, 1H), 6.65 (dd, J = 2.4 Hz, 2.7 Hz, 1H), 7.10 (d, J = 2.7 Hz, 1H), 7.27–7.31 (m, 2H), 7.42 (d, J = 7.5 Hz, 1H), 7.50 (t, J = 14.1 Hz, 3H), 7.66–7.72 (m, 4H), 7.81–7.90 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.4, 23.1, 33.3, 42.3, 55.9, 96.9, 105.9, 113.7, 113.8, 115.8, 116.9, 123.0, 124.0, 125.5, 126.8, 127.3, 127.9, 129.1, 129.3, 131.7, 133.2, 137.3, 140.4, 142.0, 152.4, 153.1, 159.8, 162.5. LC-MS (APCI+) m/z 502 $[M + 1]^+$.

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