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Tributyltin hydride-mediated straightforward synthesis of a new isoxazolo-benzazulene ring system☆

Vijay Singh and Sanjay Batra*

Medicinal Chemistry Division, Central Drug Research Institute, PO Box 173, Lucknow 226 001, India

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Abstract—Tributyltin hydride-mediated straightforward synthesis of a new isoxazolo-benzazulene system from the derivatives afforded by the Baylis–Hillman reaction of 3-(2-bromophenyl)-4-isoxazolecarbaldehydes is described.

Isoxazole is a privileged aromatic heterocycle, since its derivatives have been used as key intermediates in organic synthesis[1] and are known to be associated with a wide spectrum of biological activities.[2] These reasons have maintained the development of the chemistry of isoxazole derivatives.[3] Our interest in isoxazoles relates to the Baylis–Hillman reaction of different isoxazolecarbaldehydes and exploration of the chemistry and biological activity of the resulting derivatives.[4]

Recently, we reported the synthesis of a new isoxazole-benzazepinone ring system from the acetyl derivative of the Baylis–Hillman adducts of 4-isoxazolecarbaldehydes.[5] In continuation of our work on the synthesis of isoxazole-annulated architectures, we envisaged the synthesis of a novel isoxazolo-benzazulene system from the derivatives of the Baylis–Hillman adducts of 3-(2-bromophenyl)-4-isoxazolecarbaldehyde. In principle, radical-promoted intramolecular cyclization involving the 2-bromo group of the phenyl ring present at the 3-position of the isoxazole and the double bond of the carbon chain at C-4 using tributyltin hydride should furnish the desired ring system. A literature survey revealed that tributyltin hydride-promoted intramolecular cyclizations of derivatives of Baylis–Hillman adducts have been carried out earlier.[6] Corey and co-workers accomplished the synthesis of salinsporamide A via radical-chain cyclization[6a] while Shanmugam and Rajasingh described the construction of tetrahydrofurans[6b] and tetrahydropyrans[6c] through intramolecular vinyl radical-cyclization. However, the intramolecular cyclization involving a halide on the phenyl ring and the methylene group of the Baylis–Hillman adduct in the presence of tributyltin hydide has not been reported. Therefore, to examine this possibility we carried out the reactions of the Baylis–Hillman adducts of 3-(2-bromophenyl)-5-methyl-4-isoxazolecarbaldehyde and its corresponding derivatives with tributyltin hydride. This successfully led to the straightforward formation of the expected isoxazole-annulated ring system in fair yields. Details of the results of our preliminary investigation are disclosed in this letter.

The preparation of the starting Baylis–Hillman adducts **1**,**3a**–**c** and **2a**,**c**, was accomplished following the reported procedure.[4e] Initially, treatment of compound **1a** with tributyltin hydride in the presence of AIBN in toluene at reflux yielded a mixture of products. Purification of this mixture led to the isolation of two products. Spectral analysis confirmed the structure of the major product as the expected isoxazole-annulated benzazulene **4a** as mixture of diastereoisomers (1:1 based on NMR), while the minor product was found to be dehalogenated **5a** (Scheme 1).[7] The isolation of **5a** was intriguing, as it was expected that tributyltin hydride might abstract the halide from the phenyl ring and could simultaneously add a hydride to the methylene group. In order to ascertain unambiguously the structure of **5a**, an authentic sample of this compound was prepared from 3-phenyl-5-methyl-4-isoxazolecarbaldehyde.[4a] The generality of the reaction was confirmed by carrying out

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* Corresponding author. Tel.: +91 522 2262411 18x4368; fax: +91 522 2623405/2623938; e-mail: batra_san@yahoo.co.uk

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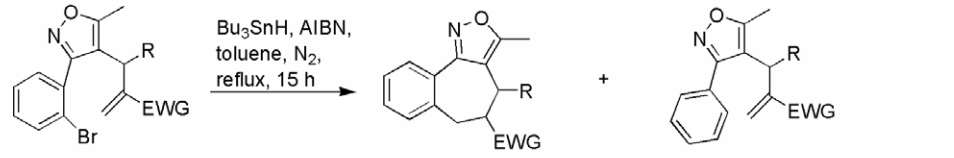

1a R= OH, EWG= CO_2Me | **4a** R= OH, EWG= CO_2Me (48%) | **5a** R= OH, EWG= CO_2Me (31%)
1b R= OH, EWG= CO_2Et | **4b** R= OH, EWG= CO_2Et (45%) | **5b** R= OH, EWG= CO_2Et (28%)
1c R= OH, EWG= CN | **4c** R= OH, EWG= CN (45%) | **5c** R= OH, EWG= CN (33%)
2a R= OAc, EWG= CO_2Me | **6a** R= OAc, EWG= CO_2Me (42%) | **7a** R= OAc, EWG= CO_2Me (15%)
2c R= OAc, EWG= CN | **6c** R= OAc, EWG= CN (40%) | **7c** R= OAc, EWG= CN (11%)
3a R= H, EWG= CO_2Me | **8a** R= H, EWG= CO_2Me (43%) | **9a** R= H, EWG= CO_2Me (22%)
3b R= H, EWG= CO_2Et | **8b** R= H, EWG= CO_2Et (47%) | **9b** R= H, EWG= CO_2Et (25%)
3c R= H, EWG= CN | **8c** R= H, EWG= CN (50%) | **9c** R= H, EWG= CN (18%)

Scheme 1.

similar reactions on compounds **1b–c** to afford the corresponding products **4b**, **c** and **5b** and **c**. However, replacing the bromine with chlorine led to failure of the reaction in these substrates and recovery of the starting materials.

In view of these results, we decided to investigate the derivatives of the Baylis–Hillman adducts of 3-(2-bromo)-4-isoxazolecarbaldehyde for the analogous reaction. Therefore, the acetyl derivatives **2a**,**c** were treated with tributyltin hydride in a similar fashion. This reaction also led to a mixture of two products, which were separated via column chromatography to afford compounds **6a**,**c** and **7a**,**c**. The isolation of compounds **7a**,**c** indicated that here too a highly chemoselective side-reaction occurs wherein the halogen on the phenyl ring is substituted with hydride. With a view to further enhance the scope of this strategy; compounds **3a–c**, obtained from the reduction of the acetate derivatives of the Baylis–Hillman adducts with sodium borohydride were reacted with tributyltin hydride. As expected, these substrates also furnished the isoxazolo-benzazulenes **8a–c** in moderate yields along with debrominated products **9a–c** in minor yields.

In summary, we have demonstrated a simple and convenient strategy for the synthesis of a novel isoxazolo-benzazulene system from the Baylis–Hillman derivatives of 3-(2-bromophenyl)-5-methyl-4-isoxazolecarbaldehyde.

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7. The NMR data for all the compounds described herein is for diastereoisomers. *General procedure for the tributyltin hydride-mediated reaction*—A mixture of appropriate bromo-derivative **1**–**3**, 2 equiv of tributyltin hydride and a catalytic amount of AIBN in anhydrous toluene was heated at reflux under nitrogen. The reaction was maintained at reflux until complete disappearance of the starting material (15 h, preferably overnight). The solvent was removed and the crude product was purified via silica gel column chromatography using hexane–EtOAc (80:20 v/v for **4** and 90:10 v/v for **6** and **8**) to afford pure products. *4-Hydroxy-3-methyl-5,6-dihydro-4H-2-oxa-1-aza-benzo[e]azulene-5-carboxylic acid methyl ester* **4a**—yellow oil; ν_{max} (neat) 1731 (CO_2Me), 3396 (OH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) $\delta = 2.56$ (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 2.97–3.11 (m, 4H, $2 \times CH_2$), 3.38–3.60 (m, 2H, $2 \times CHCO_2CH_3$), 3.76 (s, 3H, CO_2CH_3), 3.77 (s, 3H, CO_2CH_3), 5.14–5.24 (m, 2H, $2 \times CHOH$), 7.29–7.37 (m, 6H, 2×3ArH), 7.90–8.13 (m, 1H, ArH), 8.15–8.17 (m, 1H, ArH); mass (ES+) *m*/*z* 274.2 (M^++1). Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13. Found: C, 65.76; H, 5.59; N, 5.28. *2-[Hydroxy-(5-methyl-3-phenyl-isoxazol-4-yl)-methyl]-acrylic acid methyl ester* **5a**-colourless oil; ν_{max} (neat) 1719 (CO_2Me), 3407 (OH) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 2.48$ (s, 3H, CH_3), 2.96 (br s, 1H, OH), 3.73 (s, 3H, CO_2CH_3), 5.62 (s 1H, $CHOH$), 5.74 (s, 1H, =CH), 6.32 (s, 1H, =CH), 7.41–7.47 (m, 3H, ArH), 7.56–7.61 (m, 2H, ArH); mass (FAB+) *m*/*z* 274 (M^++1). Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13%. Found: C, 65.89; H, 5.50; N, 5.22%. *4-Hydroxy-3-methyl-5,6-dihydro-4H-2-oxa-1-aza-benzo[e]azulene-5-carboxylic acid ethyl ester* **4b**-yellow oil; ν_{max} (neat) 1715 (CO_2Et), 3377 (OH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) $\delta = 1.14$–1.42 (m, 6H, $2 \times CH_3CH_2$), 2.57 (two s merged, 6H, $2 \times CH_3$), 3.02–3.09 (m, 4H, $2 \times CH_2$), 3.31–3.44 (m, 2H, $2 \times CHCO_2Et$), 4.18–4.27 (m, 4H, $2 \times CH_2CH_3$), 5.15–5.22 (m, 2H, $2 \times CHOH$), 7.34–7.46 (m, 6H, 2×3ArH), 7.91–7.95 (m, 1H, ArH), 8.14–8.18 (m, 1H, ArH); mass (ES+) *m*/*z* 288.1 (M^++1). Anal. Calcd. for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.88. Found: C, 67.08; H, 6.05; N, 4.96. *4-Hydroxy-3-methyl-5,6-dihydro-4H-2-oxa-1-aza-benzo[e]azulene-5-car- bonitrile* **4c**—white solid, mp 170–172 °C; ν_{max} (KBr) 2244 (CN), 3336 (OH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) $\delta = 2.54$ (s, 3H, CH_3), 2.58 (s, 3H, CH_3), 3.01–3.09 (m, 2H, CH_2), 3.24–3.32 (m, 2H, CH_2) 3.43–3.55 (m, 2H, $2 \times CHCN$), 5.03 (br s, 2H, $2 \times OH$), 5.75–5.78 (m, 2H, $2 \times CHOH$), 7.31–7.42 (m, 6H, 2×3ArH), 7.99–8.11 (m, 2H, 2×1ArH); ^{13}C NMR (50.32 MHz, $CDCl_3$) $\delta = 17.0$, 37.6, 37.8, 42.8, 43.5, 68.7, 71.0, 107.8, 112.1, 118.4, 125.3, 132.9, 133.2, 133.5, 135.3, 135.4, 135.6, 135.7, 141.3, 142.3, 163.8, 163.9, 174.9, 175.4; mass (ES+) *m*/*z* 241.2 (M^++1). Anal. Calcd. for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 70.23; H, 5.26; N, 11.47. *4-Acetoxy-3-methyl-5,6-dihydro-4H-2-oxa-1-aza-benzo[e]azulene-5-carboxylic acid methyl ester* **6a**—yellow oil; ν_{max} (neat) 1725 (CO_2Me and OCOMe) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) $\delta = 1.96$ (s, 3H, $OCOCH_3$), 2.48 (s, 3H, CH_3), 3.11–3.17 (m, 2H, CH_2), 3.39–3.52 (m, 1H, $CHCO_2CH_3$), 3.72 (s, 3H, CO_2CH_3), 6.43 (d, 1H, $J = 3.2$ Hz, $CHOCOCH_3$), 7.31–7.43 (m, 3H, ArH), 8.06–8.10 (m, 1H, ArH); mass (ES+) *m*/*z* 316.1 (M^++1). Anal. Calcd for $C_{17}H_{17}NO_5$: C, 64.75; H, 5.43; N, 4.44. Found: C, 65.03; H, 5.52; N, 4.56. *Acetic acid 5-cyano-3-methyl-5,6-dihydro-4H-2-oxa-1-aza-benzo[e]azulen-4-yl ester* **6c**—yellow oil; ν_{max} (neat) 1749 (OCOMe), 2221 (CN) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) $\delta = 2.11$ (s, 3H, $OCOCH_3$), 2.52 (s, 3H, CH_3), 3.19–3.29 (m, 2H, CH_2), 3.43–3.48 (m, 1H, CHCN), 6.14 (d, 1H, $J = 5.2$ Hz, $CHOCOCH_3$), 7.29–7.35 (m, 1H, ArH), 7.41–7.45 (m, 2H, ArH), 7.97–8.01 (m, 1H, ArH); mass (ES+) *m*/*z* 283.2 (M^++1). Anal. Calcd for $C_{16}H_{14}N_2O_3$: C, 68.07; H, 5.00; N, 9.92. Found: C, 68.23; H, 5.12; N, 9.88. *3-Methyl-5,6-dihydro-4H-2-oxa-1-aza-benzo[e]azulene-5-carboxylic acid methyl ester* **8a**—yellow oil; ν_{max} (neat) 1731 (CO_2Me) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$)$\delta = 2.44$ (s, 3H, CH_3), 2.62–2.81 (m, 2H, CH_2), 2.89–2.99 (m, 2H, CH_2), 3.12–3.15 (m, 1H, $CHCO_2Me$), 3.73 (s, 3H, CO_2CH_3), 7.35–7.37 (m, 3H, ArH), 7.78–7.80 (m, 1H, ArH); mass (ES+) *m*/*z* 258.2 (M^++1). Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.23; H, 6.02; N, 5.56. *3-Methyl-5,6-dihydro-4H-2-oxa-1-aza-benzo[e]azulene-5-carboxylic acid ethyl ester* **8b**—yellow oil; ν_{max} (neat) 1741 (CO_2Et) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) $\delta = 1.26$ (t, 3H, $J = 7.1$ Hz, CH_3CH_2), 2.52 (s, 3H, CH_3), 2.60–2.85 (m, 2H, CH_2), 2.85–3.05 (m, 2H, CH_2), 3.20–3.32 (m, 1H, $CHCO_2Et$), 4.21 (q, 2H, $J = 7.2$ Hz, CH_2CH_3), 7.28–7.41 (m, 3H, ArH), 7.66–7.81 (m, 1H, ArH); mass (ES+) *m*/*z* 272.0 (M^++1). Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.49; H, 6.02; N, 5.23%. *3-Methyl-5,6-dihydro-4H-2-oxa-1-aza-benzo[e]azulene-5-carbonitrile* **8c**—white solid, mp 120–122 °C; ν_{max} (KBr) 2235 (CN) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) $\delta = 2.46$ (s, 3H, CH_3), 2.75–2.83 (m, 2H, CH_2), 2.97–3.04 (m, 2H, CH_2), 3.29–3.35 (m, 1H, CHCN), 7.33–7.45 (m, 3H, ArH), 7.77–7.81 (m, 1H, ArH); ^{13}C NMR (50.32 MHz, $CDCl_3$) $\delta = 10.4$, 23.3, 30.2, 34.6, 108.4, 120.9, 127.4, 127.8, 128.8, 129.7, 130.0, 134.5, 161.6, 165.2; mass (ES+) *m*/*z* 225.2 (M^++1). Anal. Calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found: C, 75.23; H, 5.48; N, 12.54.