Tetrahedron Letters, 47, 7043 (2006)

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

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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 intermediate in organic synthesis[1] and are known to be associated with wide spectrum of biological activities.[2] These reasons perhaps have kept the development of chemistry of isoxazole derivatives a continuing research endeavor.[3] Our interest in the isoxazole relates to the Baylis-Hillman reaction of different isoxazolecarbaldehydes and exploration of the chemistry and biological activity of the afforded derivatives.[4]

Recently, we have reported the synthesis of a new isoxazole-benzazepinone ring system from acetyl derivative of the Baylis-Hillman adducts of 4-isoxazolecarbaldehydes.[5] In continuation of our project on the synthesis of novel isoxazole-annulated architectures, we envisaged the synthesis of novel isoxzolo-benzazulene system from the derivatives of the Baylis-Hillman adducts of 3-(2-bromophenyl)-4-isoxazolecarbaldehyde. In principle, the radical-promoted intramolecular cyclization involving the 2-bromo group of the phenyl ring present at 3-position of the isoxazole ring and the double bond of the carbon chain at 4-position via tributyltin hydride should furnish the desired ring system. The literature survey revealed that tributyltin hydride-promoted intramolecular cyclizations in derivatives of Baylis-Hillman adduct have been carried out earlier.[6] Corey and coworkers have accomplished the synthesis of salinsporamide A involving radical-chain cyclization[6a] while Shanmugam and Rajasingh have described the construction of tetrahydrofurans[6b] and tetrahydropyrans[6c] via intramolecular vinyl radical-cyclization. However, the intramolecular cyclization involving halide of 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 the possibility we have 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 has successfully led to a straightforward formation of the expected isoxazole-annulated ring system in fair yields. The details of the results of our preliminary investigation are being disclosed in this communication.

The preparation of the starting Baylis-Hillman adducts **1,3a-c** and **2a,c**, was accomplished following the reported procedure.[4e] Initially, the treatment of compound **1a** with tributyltin hydride in the presence of AIBN in toluene at reflux temperature yielded a mixture of products. The purification of this mixture led to the isolation of two products. The spectral analysis led to establish the structure of the major product as the expected isoxazole-annulated benzazulene **4a** as mixture of diastereoisomers, while the minor product was found to be **5a** (scheme 1).[7] The isolation of **5a** was intriguing, as it was expected that tributyltin hydride may abstract the halide from the phenyl ring and could simultaneously add a hydride on the methylene group. In order to unambiguously ascertain the structure of **5a**, authentic sample of this compound was prepared from 3-phenyl-5-methyl-4-isoxazolecarbaldehye. The generality of the reaction was confirmed by carrying out similar reaction of compounds **1b-c** to afford the corresponding products **4b-c** and **5b-c**. However, replacing the halide from bromo to chloro led to failure of reaction in these substrates and the starting material was recovered.

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[*] CDRI communication no. 7020

Keywords- 5,6-Dihydro-4*H*-2-oxa-1-aza-benzo[e]azulene, tributyltin hydride, Baylis-Hillman, 4-isoxazolecarbaldehyde

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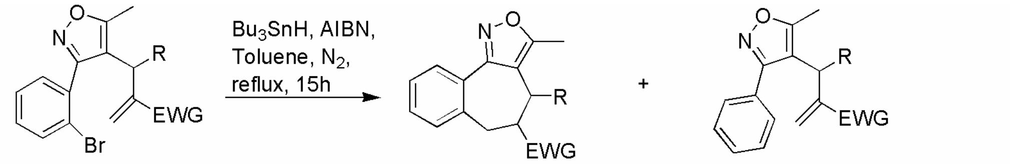
In view of these results, we decided to investigate the derivatives of the Baylis-Hillman adducts of 3-(2-bromo)-4-isoxazolecarbaldehyde for the analogous reaction. Therefore, the acetyl derivatives **2a,c** were treated with tributyltin hydride in a similar fashion. This reaction also led to a mixture of two products, which were separated via column chromatography to afford compounds **6a,c** and **7a,c**. The isolation of compound **7a,c** indicated that here too a highly chemoselective side-reaction occurs wherein the halogen on the phenyl ring is substituted with the hydride. With a view to further enhance the scope of the strategy; compounds **3a-c** obtained from the S_N2 reaction of sodium borohydride on the acetyl derivatives of Baylis-Hillman adducts were reacted with tributyltin hydride. Expectedly, these substrates too furnished the isoxazolo-benzazulenes **8a-c** in moderate yields along with debrominated products **9a-c** in minor yields.



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%)

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

Acknowledgments

One of the authors (VS) acknowledges the financial support from DST in the form of fellowship. This work was supported by the financial grant under DST Project no. SR/SI/OC-04/2003.

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7. **General procedure for the tributyltin hydride-mediated reaction-** A mixture of appropriate bromo-derivative from **1-3**, 2 equiv. of tributyltin hydride and catalytic amount of AIBN in anhydrous toluene was heated at reflux temperature under nitrogen atmosphere. The reaction was maintained at reflux until complete disappearance of starting material (15 h, preferably overnight). The solvent was removed and crude the 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)-** as yellow oil; ν_{max} (Neat) 1731 (CO_2Me), 3396 (OH) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ= 2.56 (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 2.97-3.11 (m, 4H, 2 x CH_2), 3.38-3.60 (m, 2H, 2 x $C\mathit{H}CO_2CH_3$), 3.76 (s, 3H, CO_2CH_3), 3.77 (s, 3H, CO_2CH_3), 5.14-5.24 (m, 2H, 2 x $C\mathit{H}OH$), 7.29-7.37 (m, 6H, 2 x 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. **4-Hydroxy-3-methyl-5,6-dihydro-4H-2-oxa-1-aza-benzo[e]azulene-5-carboxylic acid ethyl ester (4b)-** as yellow oil; ν_{max} (Neat) 1715 (CO_2Et), 3377 (OH) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ= 1.14-1.42 (m, 6H, 2 x $C\mathit{H}_3CH_2$), 2.57 (two s merged, 6H, 2 x CH_3), 3.02-3.09 (m, 4H, 2 x CH_2), 3.31-3.44 (m, 2H, 2 x $C\mathit{H}CO_2Et$), 4.18-4.27 (m, 4H, $C\mathit{H}_2CH_3$), 5.15-5.22 (m, 2H, 2 x $C\mathit{H}OH$), , 7.34-7.46 (m, 6H, 2 x 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-carbonitrile (4c)-** as white solid, mp 170-172^{o}C; ν_{max} (KBr) 2244 (CN), 3336 (OH) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ= 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 x CHCN), 5.03 (brs, 2H, 2 x OH), 5.75-5.78 (m, 2H, 2 x $C\mathit{H}OH$), 7.31-7.42 (m, 6H, 2 x 3ArH), 7.99-8.11 (m, 2H, 2 x 1ArH); ^{13}C NMR (50.32 MHz, $CDCl_3$,) δ= 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)-** as yellow oil; ν_{max} (Neat) 1725 (CO_2Me and OCOMe) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ= 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, $C\mathit{H}CO_2CH_3$), 3.72 (CO_2CH_3), 6.43 (d, 1H, *J*= 3.2 Hz, $C\mathit{H}OCOCH_3$), 7.31-7.43 (m, 3H, ArH), 8.06-8.10 (m, 2H, 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)-**as yellow oil; ν_{max} (Neat) 1749 (OCOMe), 2221 (CN) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ= 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, $C\mathit{H}OCOCH_3$), 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)-** as yellow oil; ν_{max} (Neat) 1731 (CO_2Me) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ= 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, $C\mathit{H}CO_2Me$), 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)-** as yellow oil; ν_{max} (Neat) 1741 (CO_2Et) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ= 1.26 (t, 3H, *J*= 7.1 Hz, $C\mathit{H}_3CH_2$), 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, $C\mathit{H}CO_2Et$), 4.21 (q, 2H, *J*= 7.2 Hz, $C\mathit{H}_2CH_3$), 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)-** as white solid, mp 120-122^{o}C; ν_{max} (KBr) 2235 (CN) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ= 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, $CDCl_3$) δ= 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.