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A novel metal-free synthesis of 6*H*-isoindolo[2,1-α]indol-6-one

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Abstract

6*H*-Isoindolo[2,1-α]indol-6-one, a core structure for a number of biologically active compounds, was synthesized in four steps. The approach is metal-free and uses a Beckmann rearrangement followed by an intramolecular cyclization.

Keywords: Beckmann rearrangement; intramolecular cyclization; 6*H*-isoindolo [2,1-*a*]indol-6-one.

Introduction

6*H*-Isoindolo[2,1-α]indol-6-one (**1**) is a core structure for a number of biologically active compounds (Boussard et al., 2006; Guillaumel et al., 2006; Samosorn et al., 2006; Ambrus et al., 2008). Indole-based structures derived from heterocyclic systems resembling 6*H*-isoindolo[2,1-α]indol-6-one (**1**) have been used as melatonin MT_3 ligands (**3**) (Boussard et al., 2006) and potential anti-tumor agents (**4**) (Guillaumel et al., 2003, 2006) as well as intermediate (**5**) in the synthesis of bacterial NorA efflux pump inhibitors (Samosorn et al., 2006; Ambrus et al., 2008) (Figure 1). A number of routes for the synthesis of 6*H*-isoindolo[2,1-α]indol-6-one (**1**) and its analogs have been reported (Carruthers and Evans, 1974; Itahara, 1981; Dalton et al., 1983; Hooper and Imam, 1985; Kozikowski and Ma, 1991; Tierney and Grinstaff, 2000; Garcia et al., 2001; Kim et al., 2003; Dwight et al., 2007; Crawford et al., 2008; Lié gault et al., 2008).

To our best knowledge, most of the strategies described in the literature involve the use of indole-based compounds as the starting materials and expensive metal catalysts (Guillaumel et al., 2003, 2006). We herein report an efficient method that does not rely on an indole starting material and costly metal catalysts.

Results and discussion

The synthesis began with a relatively cheap, commercially available starting material dibenzocyclohepten-5-one (**5**). Through reaction with hydroxylamine, oxime **6** was formed in 93% yield following standard procedures using dry pyridine as the solvent (Scheme 1) (Yale and Sowinski, 1969).

The true challenge of this route was to establish the Beckmann rearrangement reaction conditions that would provide a convenient purification method due to the extremely poor solubility of lactam **7**. The standard Beckmann rearrangement conditions, heating the oxime in polyphosphoric acid, yielded a black solid that was insoluble in number of organic solvents including acetone, methanol, ethyl acetate, and hexanes, and had poor solubility in DMF and DMSO as well (Yale and Sowinski, 1969). As a solution, we discovered that the Beckmann rearrangement could be achieved by refluxing the oxime intermediate **6** in trifluoro acetic acid (TFA), which led to the desired lactam **7** in 95% yield (Ronchin and Vavasori, 2009). The work up procedure consisted of simple evaporation of the TFA followed by silica gel column chromatography. Subsequent bromination through addition of molecular bromine to a suspension of lactam **7** in dichloromethane (DCM) (Debets et al., 2010) led to 9,10-dibromodibenzo[*b,f*]azocin-6-one (**8**) in 67% yield. The last step involved intramolecular cyclization under basic conditions and elimination of hydrogen bromide (Scheme 2). This was accomplished by dissolving compound **8** in THF followed by the slow addition of an excess amount of a base. A number of bases were studied to optimize this intramolecular cyclization/elimination reaction: *t*-BuOK, LDA, KHMDS, and triethylamine (TEA). The base that gave the best yields was TEA (70% yield). The yields for the reactions using other bases ranged from 0–47%.

Conclusions

We have developed a new four-step synthetic route (Scheme 1) to isoindolo[2,1-*a*]indol-6-one (**1**) with an overall yield of 42%. The described route is efficient and metal free, and allowed for the *de novo* construction of the indole and isoindole rings.

Experimental

Dibenzocyclohepten-5-one (**1**) was purchased form TCI America (Portland, OR, USA), and directly used without further purification. Other compounds and solvents were purchased from Acros (New Jersey, USA) and Aldrich (St. Louis MO, USA). Analytical grade solvents were used for all reactions. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400 NMR spectrometer in a deuterated solvent with TMS (δ=0.00 ppm) or the NMR solvent as the internal reference. The deuterated solvents for NMR were purchased from Cambridge Isotope Laboratories, Inc. (Andover, MA, USA), Mass spectra were recorded on an API 3200 LC/MS/MS system.

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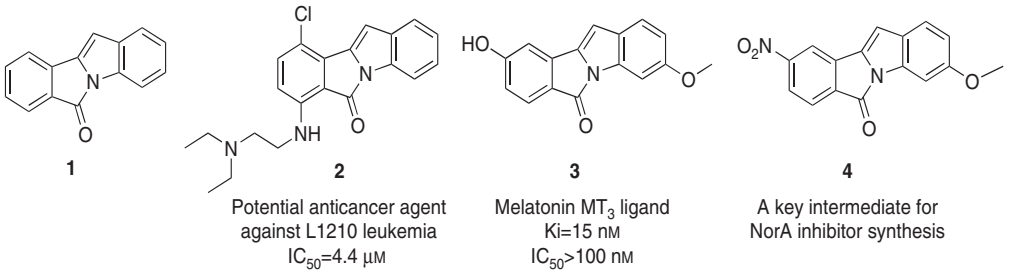
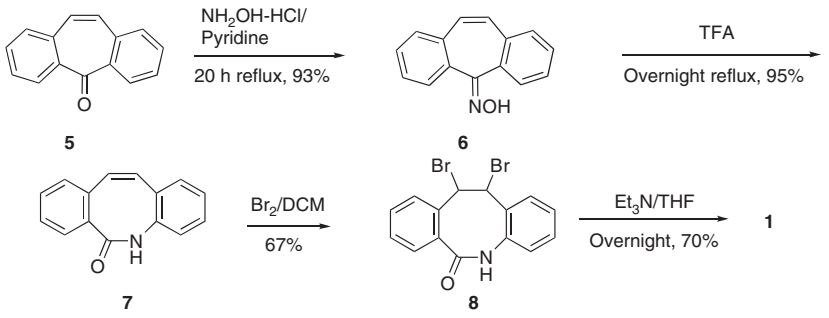
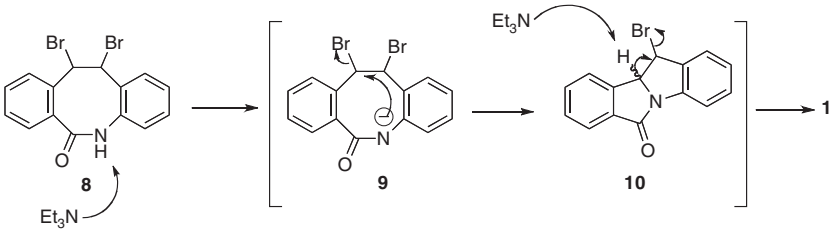


Figure 1 Chemical structures of 6*H*-isoindolo[2,1-α]indol-6-one and some biologically relevant analogs.



Scheme 1 Synthetic route to the desired 6*H*-isoindolo[2,1-α]indol-6-one.



Scheme 2 Proposed mechanism for the intramolecular cyclization/elimination of **8**.

Dibenzocyclohepten-5-one oxime (6)

A mixture of dibenzocyclohepten-5-one (**5**) (2.0 g, 9.65 mmol), hydroxylamine hydrochloride (1.0 g, 14.47 mmol), and dry pyridine (12 ml) was heated under reflux for 20 h. The pyridine in the reaction mixture was removed through evaporation *in vacuo* and the residue was poured into hexanes followed by acidification with 1 M hydrochloric acid. The two layers were placed in an ice bath for 2 h, which lead to precipitation. The solid was filtered and re-crystallized in hexanes to give a white powder product (1.9 g, 93% yield). The compound was characterized by ^{1}H NMR and MS (Yale and Sowinski, 1969).

Dibenzo[*b,f*]azocin-6-one (7)

A round-bottom flask was charged with dibenzocyclohepten-5-one oxime (**6**) (100 mg, 0.45 mmol) and TFA (5 ml). The reaction mixture was heated under reflux overnight. The TFA was evaporated and the resulting product was purified via silica gel column chromatography, using a mixture of hexanes and ethyl acetate in a 4:1 ratio as an eluent to give a grey powder product (92 mg, 95% yield). The compound was characterized by ^{1}H NMR and MS (Yale and Sowinski, 1969).

9,10-Dibromodibenzo[*b,f*]azocin-6-one (8)

Dibenzo[*b,f*]azocin-6-one (**7**) (100 mg, 0.45 mmol) was suspended in dry DCM (3 ml) and cooled to 0°C. Bromine (30 μl, 0.54 mmol) was slowly added in and the reaction mixture was stirred for 3 h at room temperature. The mixture was quenched by the addition of saturated sodium sulfite aqueous solution (1 ml). The organic and the aqueous layers were separated and the aqueous solution was extracted using DCM (3×5 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The product was eluted from silica gel column chromatography with a solvent consisting of hexanes and ethyl acetate in a 6:1 ratio to give a light-brown powder product (116 mg, 67% yield). At this point the product consisted of a mixture of stereoisomers, and was used in the next step without further purification. ^{1}H NMR (DMSO–d^6): δ 10.28 (s, 1H), 7.75–7.69 (m, 1H), 7.68–7.41 (m, 1H), 7.40–7.02 (m, 5H), 5.98–5.81 (m, 2H). MS (ESI); m/z calculated $C_{15}H_{11}Br_2NO$ $[M+H]^+$: 382.06; found: 381.90.

6*H*-isoindolo[2,1-α]indolo-6-one (1)

9,10-Dibromodibenzo[*b,f*]azocin-6-one (**8**) (50 mg, 0.131 mmol) was dissolved in dry THF (5 ml). Triethylamine (2.7 ml) was slowly added to the reaction mixture. After stirring at room temperature overnight, water (10 ml) was added and the organic layer was separated. The aqueous solution was extracted using DCM (3×10 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography with an eluent consisting of hexanes and ethyl acetate in a 5:1 ratio to give a bright yellow-green solid (20 mg, 70% yield). ^{1}H NMR ($CDCl_3$): δ 7.82 (d, *J*=8.0 Hz, 1H), 7.68 (d, *J*=7.6 Hz, 1H), 7.44–7.40 (m, 2H), 7.37 (d, *J*=7.6 Hz, 1H), 7.26–7.18 (m, 2H), 7.09 (m, 1H), 6.65 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 162.6, 138.9, 134.7, 134.5, 133.9, 133.7, 133.5, 128.8, 126.3, 125.3, 123.9, 122.3, 121.3, 113.6, 103.5. MS (ESI); m/z calculated $C_{15}H_9NO$ $[M+H]^+$: 219.07; found 219.07.

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