Tetrahedron 68 (2012) 1745–1749

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Tricyclic isoindolines by Heck cyclization

Gedu Satyanarayana [a], Martin E. Maier [b,*]

[a] Department of Chemistry, Indian Institute of Technology (IIT) Hyderabad, Ordnance Factory Estate Campus, Yeddumailaram 502205, Medak District, Andhra Pradesh, India
[b] Institut für Organische Chemie, Universität Tübingen, Auf der Morgenstelle 18, 72076 Tübingen, Germany

ARTICLE INFO

Article history:
Received 19 October 2011
Received in revised form 14 December 2011
Accepted 20 December 2011
Available online 24 December 2011

Keywords:
Heck cyclization
Isoindoles
Enamides
Heterocycles
Pyridones

ABSTRACT

A series of 4-formyl esters **8a**–**d** was prepared by Michael addition of an enamine with ethyl acrylate. A subsequent condensation with 2-bromobenzylamines **3** gave rise to cyclic enamides **9aa**–**dd**. In a Heck cyclization reaction tricyclic isoindoles **10aa**–**dd** were formed in good yields.

1. Introduction

The Heck coupling turned out to be a highly versatile C–C bond forming reaction.[1] Quite remarkably, this cross-coupling reaction takes place to all kinds of olefins. For example, both alkenes with an electron-withdrawing or -donating substituent can be employed as substrates. The regiochemistry with substituted alkenes has been studied extensively.[2] For example, intermolecular Heck coupling reactions between an aryl halide and enamides or enamines takes place geminal to the nitrogen substituent.[3] The same regiochemistry in general is observed in Heck cyclization reactions[4] (intramolecular Heck reactions) in particular if the aryl bromide is attached to the nitrogen of the enamide. For example, in the context of the synthesis of the 3-arylisoquinoline alkaloid, decumbenine B, and related compounds, Orito et al. described the cyclization of *N*-benzoyldihydroisoquinolines to dibenz[*a*,*f*]-indolizines (Fig. 1, Eq. 1).[5–7] Similar regiochemistry was observed for the cyclization of *o*-halobenzyl cyclohexenyl ethers.[8] Our own contributions to the Heck cyclization of enamides involved reactions of cyclic enamides with a (2-bromophenyl)alkyl substituent in the β-position of the enamide. We obtained spiro products that resulted from attack of the aryl palladium intermediate to the β-carbon of the enamide (Fig. 1, Eq. 2).[9] The cyclic enamides were readily obtained from 4-formyl esters by condensation with primary amines, like benzylamines.

It occurred to us that the use of 2-bromobenzylamines in the enamide forming reaction should readily give substrates for Heck cyclizations that might provide products containing an isoindole subunit. In this paper we describe the realization of this strategy.

The isoindole structure can be found in many natural and man-made compounds. For example, analogues of the antitumor compound camptothecin, so called aromathecins contain this substructure.[10] Most approaches rely on a halobenzyl moiety as a precursor to a nucleophilic group. The crucial cyclization reactions are then carried out under radical,[11] transition metal catalyzed,[5,12] or anionic conditions.[13] Another frequently used strategy employs cyclization reactions onto acyliminium ions.[14]

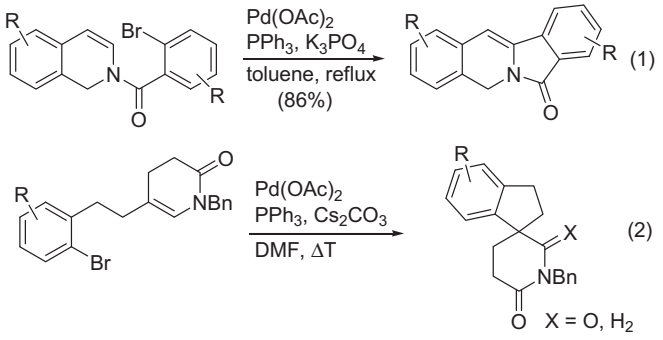


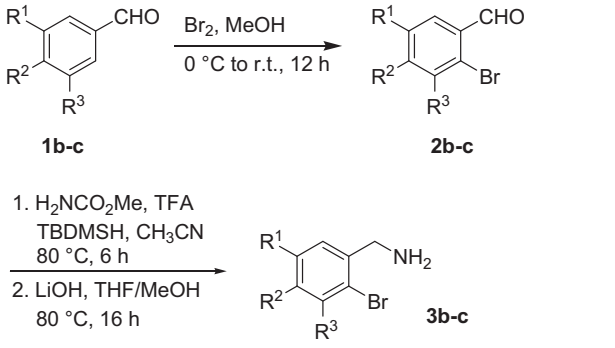
Fig. 1. Some examples of Heck reactions to enamides.

* Corresponding author. Tel.: +49 7071 2975247; e-mail address: martin.e.maier@uni-tuebingen.de (M.E. Maier).

0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.12.060

2. Results and discussion

For the purpose of the present study a range of 2-bromobenzylamines **3a**–**d** were employed. While benzylamine **3a** is commercially available, primary amines **3b**–**d** were prepared from the corresponding benzaldehydes **1b**–**d** using a reported bromination method[15] followed by a reductive amination[16] protocol (Scheme 1). Thus, the aldehydes were first converted to the corresponding methyl carbamate in presence of *tert*-butyldimethylsilane (TBDMSH) as reducing agent. Subsequent basic hydrolysis furnished the amines **3**.



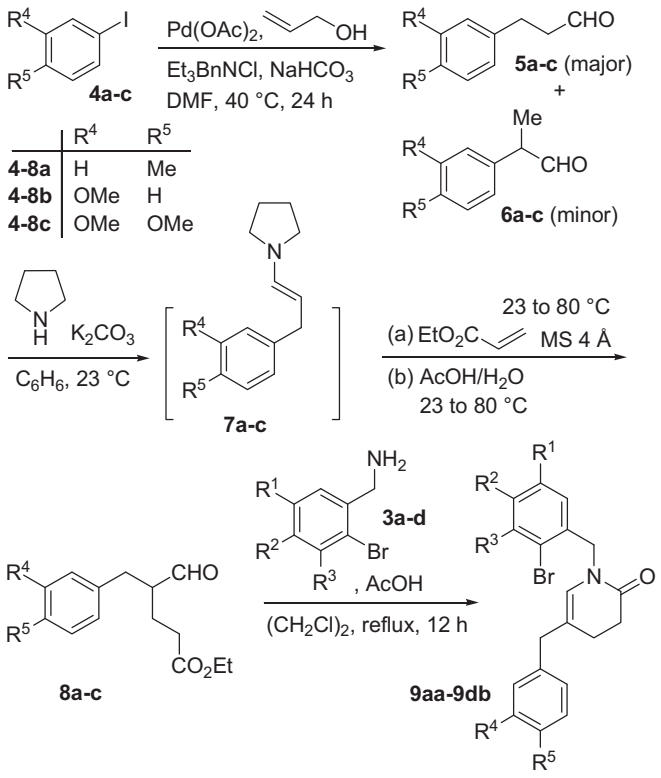
	R^1	R^2	R^3	yield (%)
3a	H	H	H	–
3b	OMe	H	H	95
3c	OMe	OMe	H	93
3d	OMe	OMe	OMe	90

Scheme 1. Synthesis of 2-bromobenzylamines **3b**–**d** from benzaldehydes **1b**–**d** via bromination, reductive carbamate formation, and hydrolysis.

The requisite cyclic enamides **9** in turn could be obtained easily using our well established synthetic strategy from 4-formyl esters **8** and benzylamines **3a**–**d**.[17] The formyl esters **8** would be obtained by Michael addition of enamines derived from aldehydes to ethyl acrylate. Initially, we prepared some propional derivatives with an aryl terminus. These were obtained by Pd-catalyzed reaction of aryl iodides **4a**–**c** with allylic alcohol.[18–21] This Heck coupling was performed under phase transfer conditions in DMF. These conditions gave rise to the corresponding arylpropanaldehydes **5a**–**c** as major products along with the minor branched isomers **6a**–**c**. Subsequently, reaction of the propanaldehydes **5a**–**c** with pyrrolidine in presence of K_2CO_3 followed by treatment of the resulting enamines **7a**–**c** with ethyl acrylate and final acid hydrolysis furnished the 4-formyl esters **8a**–**c** in good overall yields. Compound **8c** was already utilized in our previous work.[20,22] Now, acid induced cyclization of 4-formyl esters esters **8a**–**c** with the 2-bromobenzylamines **3a**–**d**, smoothly produced the desired cyclic enamides **9a**–**f** in excellent yields as depicted in Scheme 2 and Table 1.

In order to extend the generality of the strategy, we also prepared cyclic enamides **9ad**, **9bd**, and **9dd** starting from purely aliphatic octanal (capryl aldehyde) **5d**. Thus, enamine formation followed by Michael addition on capryl aldehyde **5d**, gave the corresponding 4-formyl ester **8d** in 66% yield. Acid induced cyclic enamide formation could also successfully be carried out with benzylamines **3a**–**b** and **3d**, and furnished the corresponding cyclic enamides **9ad**, **9bd**, and **9dd** in excellent yields (Scheme 3, Table 2).

With the cyclic enamides **9aa**–**dd** in hand, the key Pd-catalyzed intramolecular Heck cyclization was explored. Thus, reaction of **9aa**



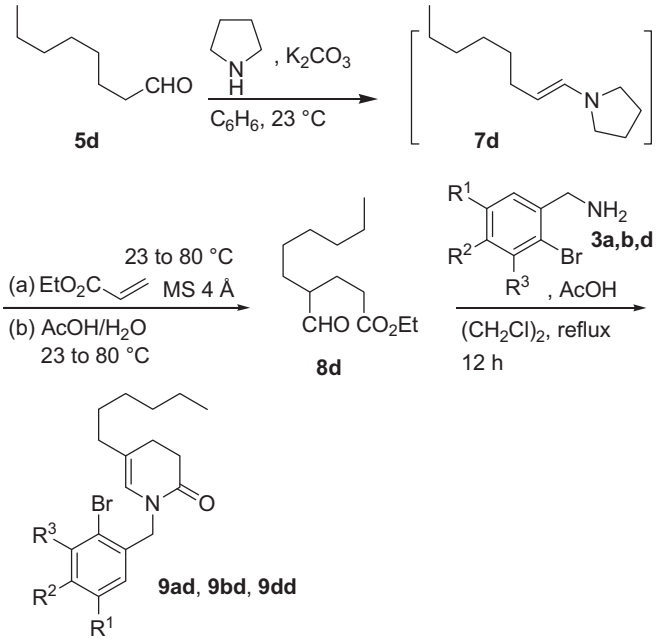
Scheme 2. Synthesis of cyclic enamides **9aa**–**db**, via Michael addition of the enamines **7a**–**c** with ethyl acrylate and cyclization of the 4-formyl esters **8a**–**c** with 2-bromobenzylamines **3a**–**d**; for compounds **9** the first letter refers to the substituents of the benzylamine part (**3a**–**d**), whereas the second letter indicates the residues coming from the aryl iodides **4a**–**c**. The first letter in the compound numbers **9** and **10** (vide infra) indicates the 2-bromobenzylamine used, the second letter refers to the aldehydes **5** and the formyl esters **8**, respectively.

Table 1
Yields for the transformations leading to piperidinones **9aa**–**db**

R^1	R^2	R^3	R^4	R^5	Coupling step [%]	Michael addition [%]	Cyclization to enamide [%]
H	H	H	H	Me	**5a** (80)	**8a** (66)	**9aa** (80)
H	H	H	OMe	H	**5b** (83)	**8b** (68)	**9ab** (86)
H	H	H	OMe	OMe	**5c** (72)	**8c** (62)	**9ac** (94)
OMe	H	H	H	Me	**5a** (80)	**8a** (66)	**9ba** (91)
OMe	OMe	H	H	Me	**5a** (80)	**8a** (66)	**9ca** (88)
OMe	OMe	OMe	OMe	H	**5b** (83)	**8b** (68)	**9db** (88)

under established reaction conditions, that is, $Pd(OAc)_2$ (10 mol %)/PPh_3 (20 mol %) in presence of the base Cs_2CO_3 (4 equiv) in dry DMF at 120 °C for 72 h furnished the tricyclic isoindole **10aa** in excellent yield 82%. It is noteworthy that the product isolated had the double bond isomerized to the thermodynamically more stable product with a tetrasubstituted double bond. Reducing the reaction time to 24 h resulted in incomplete reaction with considerable amount of starting material along with the desired isoindole **14a**. Accordingly, a longer reaction time of 72 h was applied to the other arylsubstituted cyclic enamides **9aa**–**dd**. Gratifyingly, it was found that the above reaction conditions also worked for the other cases as well leading to the products **10aa**–**dd** in good to excellent yields (60–83%). The yield was somewhat lower in case of **10db** and **10dd** where the product yields were 60% and 70%, respectively. This might be attributed to the steric demanding nature of the highly substituted aromatic moiety (Scheme 4).

In the ^1H NMR spectrum of the cyclic enamides **9** the olefinic proton at the 6-position typically appears at around 5.9 ppm as a singlet. The corresponding carbon resonates at around 125 ppm.



Scheme 3. Synthesis of cyclic enamides **9ad**, **9bd**, and **9dd** starting from octanal **5d**.

Table 2
Yields for the transformations leading to piperidinones **9ad**, **9bd**, and **9dd**

R^1	R^2	R^3	Michael addition [%]	Cyclization to enamide [%]
H	H	H	**8d** (66)	**9ad** (89)
OMe	H	H	**8d** (66)	**9bd** (89)
OMe	OMe	OMe	**8d** (66)	**9dd** (84)

In the products **10** this signal is not present, indicating the formation of the isoindole system.

After having successfully achieved the synthesis of tricyclic enamides **10ab**–**dd**, we became interested to see what would happen if both the aromatic rings contain a halogen atom at the α-position. Based on our previous findings,[17,23] one could expect the formation of unsymmetrical biaryl compounds in addition to the Heck cyclization. In order address this question, the acid induced cyclization of the 4-formyl ester[17] **8e** was carried out with 2-bromobenzylamine **3a** to generate the dibromoenamide **9ae** in very good yield of 90%. However, as it turned out the Pd-catalyzed reaction under the previously established conditions only furnished the simple tricyclic isoindole **10ac** albeit in poor yield 38% as depicted in Scheme 5. Thus, while the Heck cyclization had taken place, the bromide on the dimethoxybenzyl group was simply reductively removed.

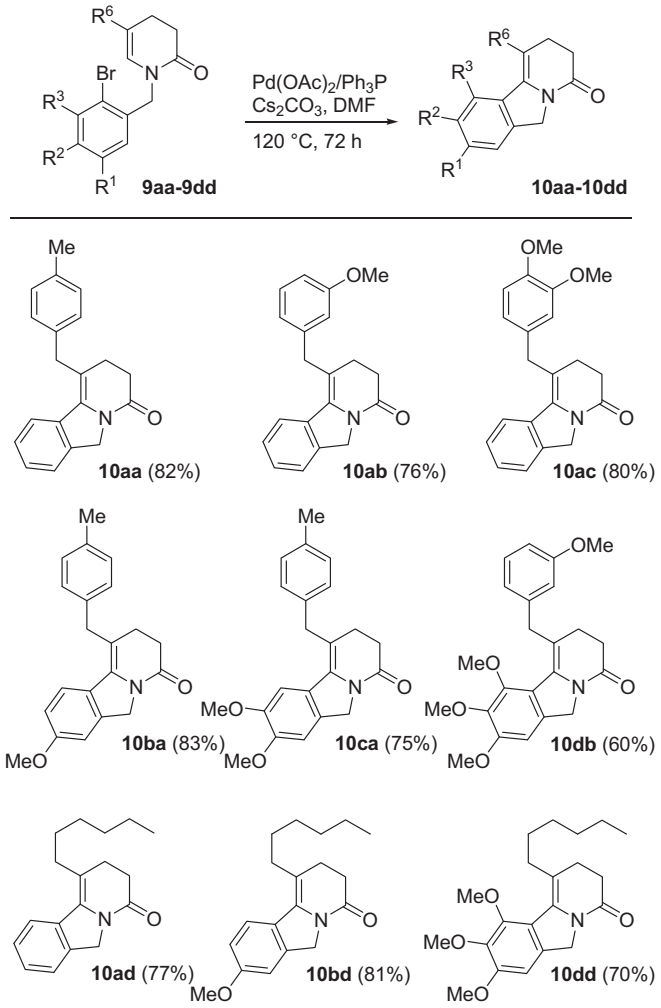
3. Conclusion

In conclusion we have developed a practical and efficient four step strategy for the synthesis of tricylic isoindoles, using the Pd-catalyzed Heck cyclization as a key transformation of the strategy. The present approach seems useful as it permits the formation of a wide range of substituted tricyclic isoindoles.

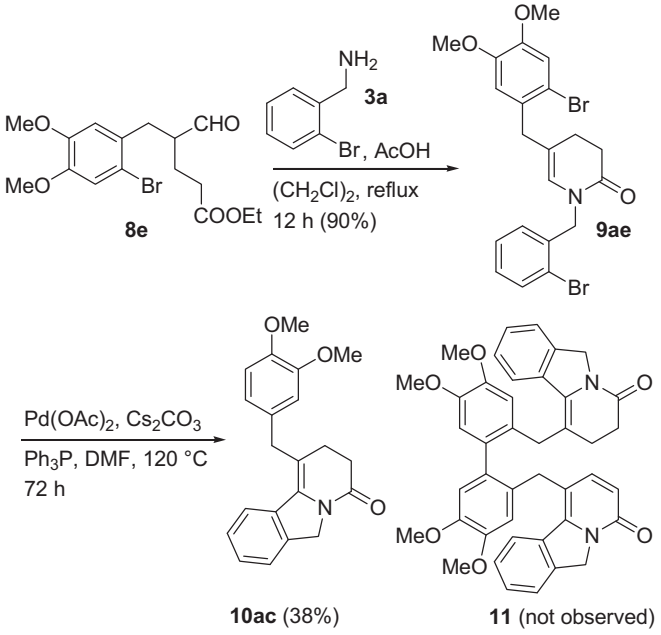
4. Experimental section

4.1. 3-(4-Methylphenyl)propanal (5a) and 2-(4-methylphenyl) propanal (6a)

To a stirred solution of $Pd(OAc)_2$ (41.2 mg, 0.18 mmol), allylalcohol (1.25 mL, 18.3 mmol), triethylbenzylammonium chloride



Scheme 4. Palladium-catalyzed transformation of the cyclic enamides **9aa**–**dd** into **10aa**–**dd**.



Scheme 5. Palladium-catalyzed cyclization of the enamide **8e** to isoindole derivative **3c**.

(2.1 g, 9.2 mmol), and $NaHCO_3$ (1.58 g, 18.3 mmol) in DMF (15 mL) was added 4-methyliodobenzene **4a** (2.0 g, 9.2 mmol) and the resulted solution was heated at 40 °C for 24 h. The reaction was quenched with aqueous NH_4Cl solution and the mixture extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with saturated NaCl solution, dried (Na_2SO_4), and filtered. Evaporation of the solvent and purification of the crude material by flash chromatography (ethyl acetate/hexane, 2:98 to 1:24) furnished the aldehyde **6a** (60 mg, 4%) as colorless oil. Further elution (ethyl acetate/hexane, 1:24 to 1:8) as eluent gave the desired propanal **5a** (1.1 g, 80%) as brown viscous oil.

Compound **5a**: R_f=0.45 (ethyl acetate/hexane, 1:9); ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.81 (s, 1H, CH═O), 7.10 (d, J=8.4 Hz, 2H, Ar−H), 7.08 (d, J=8.4 Hz, 2H, Ar−H), 2.92 (t, J=7.4 Hz, 2H, 3-H), 2.75 (t, J=7.4 Hz, 2H, 2-H), 2.31 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=201.7 (CH═O), 137.2 (C), 135.8 (C), 129.3 (2C, CH), 128.1 (2C, CH), 45.4 (C-3), 27.7 (C-2), 21.0 (CH_3).

Compound **6a**: R_f=0.6 (ethyl acetate/hexane, 1:9); ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.66 (s, 1H, CH═O), 7.19 (d, J=7.9 Hz, 2H, Ar−H), 7.09 (d, J=7.9 Hz, 2H, Ar−H), 3.60 (q, J=7.1 Hz, 1H, 2-H), 2.34 (s, 3H, $ArCH_3$) 1.42 (3H, d, J=7.1 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=201.2 (CH═O), 137.2 (C), 134.6 (C), 129.8 (2C, CH), 128.2 (2C, CH), 52.6 (C-2), 21.0 ($ArCH_3$), 14.6 (CH_3).

4.2. Ethyl 4-formyl-5-(4-methylphenyl)pentanoate (8a)

To a magnetically stirred solution of the aldehyde **5a** (1.0 g, 6.7 mmol) in benzene (7 mL) was added anhydrous K_2CO_3 (2.8 g, 20.3 mmol) followed by pyrrolidine (1.12 mL, 13.5 mmol). The reaction mixture was stirred for 6 h at room temperature. Then the mixture was treated with saturated aqueous $NaHCO_3$ solution, and extracted with diethyl ether (3×20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo to provide the crude enamine **7a**. To the crude enamine in CH_3CN (7 mL) at 5 °C were added molecular sieves (4 Å, 2 g) followed by ethyl acrylate (1.17 mL, 10.8 mmol). The resulting mixture was stirred for 2 h at room temperature, and then refluxed for 2 h. After cooling of the mixture to room temperature, AcOH (2 mL) in H_2O (8 mL) was added followed by refluxing of the mixture for 2 h. After cooling to ambient temperature, the mixture was treated with 3 N HCl, and extracted with ethyl acetate (3×20 mL). The combined organic extracts were washed with saturated NaCl solution, dried (Na_2SO_4), and filtered. Concentration of the filtrate and purification of the residue by flash chromatography (ethyl acetate/hexane, 2:98 to 1:7) furnished the aldehyde ester **8a** (1.1 g, 66% for two steps) as a colorless oil. R_f=0.45 (ethyl acetate/hexane, 1:7); ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.66 (s, 1H, CH═O), 7.09 (d, J=8.1 Hz, 2H, Ar−H), 7.04 (d, J=8.1 Hz, 2H, Ar−H), 4.10 (q, J=7.1 Hz, 2H, OCH_2CH_3), 2.96 (dd, J=13.2, 6.4 Hz, 1H, 5-H), 2.69 (dd, J=13. 2, 6.4 Hz, 5-H) 2.80−2.55 (m, 1H, 4-H), 2.45−2.20 (m, 2H, 2-H), 2.30 (3H, s, $ArCH_3$), 2.05−1.86 (m, 1H, 3-H), 1.86−1.70 (m, 1H, 3-H), 1.22 (t, J=7.1 Hz, 3H, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=203.8 (CH═O), 172.8 (OC═O), 136.1 (C), 135.0 (C), 129.3 (2C, CH), 128.8 (2C, CH), 60.5 (OCH_2CH_3), 52.5 (C-4), 34.7 (CH_2Ar), 31.5 (C-2), 23.4 (C-3), 20.9 ($ArCH_3$), 14.1 (OCH_2CH_3); due to the somewhat instable nature of the aldehydes, no HRMS data were acquired.

4.3. 1-(2-Bromobenzyl)-5-(4-methylbenzyl)-3,4-dihydropyridin-2(1*H*)-one (9aa)

To a magnetically stirred solution of the formyl ester **8a** (400 mg, 1.6 mmol) in CH_2ClCH_2Cl (5 mL) at room temperature, were added sequentially 2-bromobenzylamine **3a** (420 mg, 2.2 mmol) and AcOH (0.14 mL, 2.4 mmol) followed by refluxing of the mixture for 12 h. After cooling, the reaction mixture was treated with aqueous $NaHCO_3$ solution and extracted with ethyl acetate (3×12 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and filtered. Concentration of the filtrate followed by flash chromatography (ethyl acetate/hexane, 1:6 to 2:3) furnished the cyclic enamide **9aa** (480 mg, 80%) as brown viscous oil. R_f=0.45 (ethyl acetate/hexane, 2:3); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.55 (d, J=7.9 Hz, 1H, 3″-H), 7.29 (dd, J=7.3, 7.3 Hz, 1H, Ar−H), 7.17 (d, J=7.3 Hz, 1H, 6″-H), 7.14 (dd, J=7.3, 7.3 Hz, 1H, Ar−H), 7.09 (d, J=7.9 Hz, 2H, Ar−H), 7.02 (d, J=7.9 Hz, 2H, Ar−H), 5.86 (s, 1H, 6-H), 4.76 (s, 2H, NCH_2Ar), 3.26 (s, 2H, CH_2Ar), 2.55 (t, J=7.9 Hz, 2H, 4-H), 2.32 (s, 3H, $ArCH_3$), 2.22 (t, J=7.9 Hz, 2H, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.9 (NC═O), 136.1 (C), 136.0 (C), 135.6 (C), 132.8 (CH), 129.1 (2C, CH), 128.8 (CH), 128.6 (CH), 128.5 (2C, CH), 127.6 (CH), 125.3 (C-6), 123.2 (C-2″), 119.9 (C-5), 49.1 (NCH_2Ar), 39.6 (CH_2Ar), 31.2 (C-3), 23.9 (C-4), 21.0 (CH_3, $ArCH_3$); HRMS (ESI) calcd for $C_{20}H_{21}BrNO$ $[M+H]^+$ 370.0801, found 370.0801.

4.4. 1-(2-Bromobenzyl)-5-(4-methylbenzyl)-3,4-dihydropyridin-2(1*H*)-one (9aa)

To a magnetically stirred solution of the formyl ester **8a** (400 mg, 1.6 mmol) in CH_2ClCH_2Cl (5 mL) at room temperature, were added sequentially 2-bromobenzylamine **3a** (420 mg, 2.2 mmol) and AcOH (0.14 mL, 2.4 mmol) followed by refluxing of the mixture for 12 h. After cooling, the reaction mixture was treated with aqueous $NaHCO_3$ solution and extracted with ethyl acetate (3×12 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and filtered. Concentration of the filtrate followed by flash chromatography (ethyl acetate/hexane, 1:6 to 2:3) furnished the cyclic enamide **9aa** (480 mg, 80%) as brown viscous oil. R_f=0.45 (ethyl acetate/hexane, 2:3); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.55 (d, J=7.9 Hz, 1H, 3″-H), 7.29 (dd, J=7.3, 7.3 Hz, 1H, Ar−H), 7.17 (d, J=7.3 Hz, 1H, 6″-H), 7.14 (dd, J=7.3, 7.3 Hz, 1H, Ar−H), 7.09 (d, J=7.9 Hz, 2H, Ar−H), 7.02 (d, J=7.9 Hz, 2H, Ar−H), 5.86 (s, 1H, 6-H), 4.76 (s, 2H, NCH_2Ar), 3.26 (s, 2H, CH_2Ar), 2.55 (t, J=7.9 Hz, 2H, 4-H), 2.32 (s, 3H, $ArCH_3$), 2.22 (t, J=7.9 Hz, 2H, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.9 (NC═O), 136.1 (C), 136.0 (C), 135.6 (C), 132.8 (CH), 129.1 (2C, CH), 128.8 (CH), 128.6 (CH), 128.5 (2C, CH), 127.6 (CH), 125.3 (C-6), 123.2 (C-2″), 119.9 (C-5), 49.1 (NCH_2Ar), 39.6 (CH_2Ar), 31.2 (C-3), 23.9 (C-4), 21.0 (CH_3, $ArCH_3$); HRMS (ESI) calcd for $C_{20}H_{21}BrNO$ $[M+H]^+$ 370.0801, found 370.0801.

4.5. 1-(4-Methylbenzyl)-2,6-dihydropyrido[2,1-*a*]isoindol-4(3*H*)-one (10aa)

To a solution of bromoenamide **9aa** (100 mg, 0.3 mmol) in anhydrous DMF (2 mL), in an oven dried Schlenk tube fitted with a rubber septum, were added PPh_3 (14.2 mg, 20 mol %), Cs_2CO_3 (352 mg, 1.1 mmol), and $Pd(OAc)_2$ (6.1 mg, 10 mol %) at room temperature under nitrogen atmosphere. The stirred reaction mixture was heated in an oil bath at 120 °C for 3 days. The mixture was cooled to room temperature, treated with saturated aqueous NH_4Cl solution, and then extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with saturated NaCl solution, dried (Na_2SO_4), and filtered. Evaporation of the filtrate and purification of the crude material by flash chromatography (ethyl acetate/hexane, 1:4 to 3:2) furnished the tricyclic isoindole **10aa** (64 mg, 82%) as a colorless solid, which was recrystallized from a mixture of CH_2Cl_2 and hexane; mp 120−122 °C. R_f=0.45 (ethyl acetate/hexane, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.68 (d, J=7.1 Hz, 1H, Ar−H), 7.37 (d, J=7.1 Hz, 1H, Ar−H), 7.32 (dd, J=7.1, 7.1 Hz, 1H, Ar−H), 7.28 (dd, J=7.1, 7.1 Hz, 1H, Ar−H), 7.16 (d, J=7.9 Hz, 2H, Ar−H), 7.11 (d, J=7.9 Hz, 2H, Ar−H), 4.89 (s, 2H, NCH_2Ar), 3.85 (s, 2H, CH_2Ar), 2.52 (t, J=7.9 Hz, 2H, 3-H), 2.42 (t, J=7.9 Hz, 2H, 2-H), 2.32 (s, 3H, $ArCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.1 (NC═O), 137.6 (C), 136.0 (C), 135.4 (C), 135.3 (C), 134.1 (C), 129.3 (2C, CH), 128.3 (CH), 128.1 (2C, CH), 127.9 (CH), 123.3 (CH), 122.8 (CH), 112.0

(C), 50.0 (NCH_2Ar), 36.5 (CH_2Ar), 30.6 (CH_2), 27.1 (CH_2), 20.9 ($ArCH_3$); HRMS (ESI) calcd for $C_{20}H_{20}NO$ $[M+H]^+$ 290.1539, found 290.1539.

Acknowledgements

Financial support from the Alexander von Humboldt foundation (short term stay for G.S.) is greatly acknowledged.

Supplementary data

Procedure for remaining new compounds, copies of NMR spectra. Supplementary data related to this article can be found online at doi:10.1016/j.tet.2011.12.060.

References and notes

1. For some key reviews, see: (a) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009–3066; (b) Poli, G.; Giambastiani, G.; Heumann, A. *Tetrahedron* **2000**, *56*, 5959–5989; (c) Wu, X.-F.; Anbarasan, P.; Neumann, H.; Beller, M. *Angew. Chem.* **2010**, *122*, 9231–9234; *Angew. Chem., Int. Ed.* **2010**, *49*, 9047–9050.
2. For a recent review, see: Ruan, J.; Xiao, J. *Acc. Chem. Res.* **2011**, *44*, 614–626.
3. (a) Vallin, K. S. A.; Zhang, Q.; Larhed, M.; Curran, D. P.; Hallberg, A. *J. Org. Chem.* **2003**, *68*, 6639–6645; (b) Harrison, P.; Meek, G. *Tetrahedron Lett.* **2004**, *45*, 9277–9280; (c) Mo, J.; Liu, S.; Xiao, J. *Tetrahedron* **2005**, *61*, 9902–9907; (d) Mo, J.; Xu, L.; Xiao, J. *J. Am. Chem. Soc.* **2005**, *127*, 751–760.
4. (a) Ripa, L.; Hallberg, A. *J. Org. Chem.* **1997**, *62*, 595–602; (b) Lindstroem, S.; Ripa, L.; Hallberg, A. *Org. Lett.* **2000**, *2*, 2291–2293; (c) Aurrecoechea, J. M.; Coy, C. A.; Patiño, O. J. *J. Org. Chem.* **2008**, *73*, 5194–5197.
5. Wada, Y.; Nishida, N.; Kurono, N.; Ohkuma, T.; Orito, K. *Eur. J. Org. Chem.* **2007**, 4320–4327.
6. For an exception, see: Padwa, A.; Brodney, M. A.; Lynch, S. M. *J. Org. Chem.* **2001**, *66*, 1716–1724.
7. For further examples of Heck cyclizations of vinyl- or aryl halides to enamides, see: (a) Grigg, R.; Sridharan, V.; Stevenson, P.; Sukirthalingam, S.; Worakun, T. *Tetrahedron* **1990**, *46*, 4003–4018; (b) Nukui, S.; Sodeoka, M.; Shibasaki, M. *Tetrahedron Lett.* **1993**, *34*, 4965–4968; (c) Sato, Y.; Nukui, S.; Sodeoka, M.; Shibasaki, M. *Tetrahedron* **1994**, *50*, 371–382; (d) Comins, D. L.; Joseph, S. P.; Zhang, Y.-M. *Tetrahedron Lett.* **1996**, *37*, 793–796; (e) Yoneda, R.; Kimura, T.; Kinomoto, J.; Harusawa, S.; Kurihara, T. *J. Heterocycl. Chem.* **1996**, *33*, 1909–1913; (f) García, A.; Rodríguez, D.; Castedo, L.; Saá, C.; Domínguez, D. *Tetrahedron Lett.* **2001**, *42*, 1903–1905; (g) Kiewel, K.; Tallant, M.; Sulikowski, G. A. *Tetrahedron Lett.* **2001**, *42*, 6621–6623; (h) Fuwa, H.; Sasaki, M. *Heterocycles* **2008**, *76*, 521–539; (i) Onozaki, Y.; Kurono, N.; Senboku, H.; Tokuda, M.; Orito, K. *J. Org. Chem.* **2009**, *74*, 5486–5495.
8. Svennebring, A.; Nilsson, P.; Larhed, M. *J. Org. Chem.* **2007**, *72*, 5851–5854.
9. (a) Satyanarayana, G.; Maier, M. E. *J. Org. Chem.* **2008**, *73*, 5410–5415; (b) Satyanarayana, G.; Maichle-Mössmer, C.; Maier, M. E. *Chem. Commun.* **2009**, 1571–1573.
10. (a) Pin, F.; Comesse, S.; Sanselme, M.; Daïch, A. *J. Org. Chem.* **2008**, *73*, 1975–1978; (b) Van, H. T. M.; Cho, W.-J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2551–2554.
11. See for example: (a) Beckwith, A. L. J.; Westwood, S. W. *Tetrahedron* **1989**, *45*, 5269–5282; (b) Berteina, S.; De Mesmaeker, A. *Synlett* **1998**, 1227–1230; (c) Jabin, I.; Netchitaïlo, P. *Tetrahedron Lett.* **2001**, *42*, 7823–7827; (d) Zhang, W.; Pugh, G. *Tetrahedron* **2003**, *59*, 3009–3018; (e) Marion, F.; Courillon, C.; Malacria, M. *Org. Lett.* **2003**, *5*, 5095–5097; (f) Marion, F.; Coulomb, J.; Servais, A.; Courillon, C.; Fensterbank, L.; Malacria, M. *Tetrahedron* **2006**, *62*, 3856–3871.
12. Wang, F.; Song, G.; Du, Z.; Li, X. *J. Org. Chem.* **2011**, *76*, 2926–2932.
13. (a) Mori, M.; Hashimoto, A.; Shibasaki, M. *J. Org. Chem.* **1993**, *58*, 6503–6504; (b) Meyers, A. I.; Santiago, B. *Tetrahedron Lett.* **1995**, *36*, 5877–5880; (c) Comins, D. L.; Zhang, Y.-M. *J. Am. Chem. Soc.* **1996**, *118*, 12248–12249.
14. (a) Alsarabi, A. E.; Canet, J.-L.; Troin, Y. *Tetrahedron Lett.* **2004**, *45*, 9003–9006; (b) Zhou, Y.; Zhai, Y.; Li, J.; Ye, D.; Jiang, H.; Liu, H. *Green Chem.* **2010**, *12*, 1397–1404.
15. Chandrasekhar, S.; Reddy, N. R.; Rao, Y. S. *Tetrahedron* **2006**, *62*, 12098–12107.
16. Lehmann, F.; Scobie, M. *Synthesis* **2008**, 1679–1681.
17. See, for example: Satyanarayana, G.; Maier, M. E. *Org. Lett.* **2008**, *10*, 2361–2364.
18. (a) Jeffery, T. *Tetrahedron Lett.* **1991**, *32*, 2121–2124; (b) Wolfe, J. P.; Rennels, R. A.; Buchwald, S. L. *Tetrahedron* **1996**, *52*, 7525–7546; (c) Tietze, L. F.; Kahle, K.; Raschke, T. *Chem.—Eur. J.* **2002**, *8*, 401–407; (d) Bruyère, D.; Bouyssi, D.; Balme, G. *Tetrahedron* **2004**, *60*, 4007–4017; (e) Alacid, E.; Nájera, C. *Adv. Synth. Catal.* **2007**, *349*, 2572–2584; (f) Stone, M. T. *Org. Lett.* **2011**, *13*, 2326–2329.
19. For a review, see: Muzart, J. *Tetrahedron* **2005**, *61*, 4179–4212.
20. Satyanarayana, G.; Maier, M. E. *Tetrahedron* **2008**, *64*, 356–363.
21. For alternative preparations, see: Frost, C. G.; Hartley, B. C. *J. Org. Chem.* **2009**, *74*, 3599–3602.
22. Padwa, A.; Brodney, M. A.; Marino, J. P., Jr.; Sheehan, S. M. *J. Org. Chem.* **1997**, *62*, 78–87.
23. Satyanarayana, G.; Maier, M. E. *Eur. J. Org. Chem.* **2008**, 5543–5552.