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Tetrahedron Letters
Tetrahedron Letters 49 (2008) 363–366

Preparation of 3-substituted-2-pyridin-2-ylindoles: regioselectivity of Larock's indole annulation with 2-alkynylpyridines

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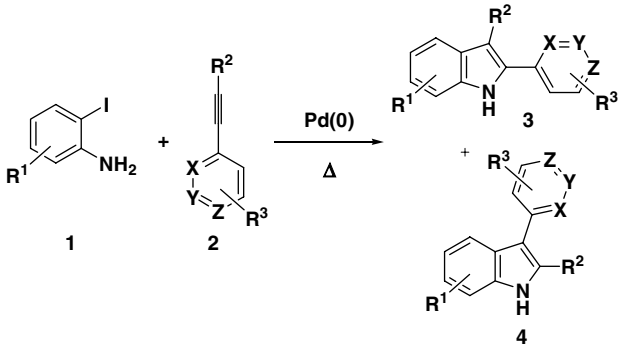
Received 10 October 2007; revised 5 November 2007; accepted 6 November 2007
Available online 13 November 2007

Abstract—A regioselective Larock approach to 3-substituted-2-pyridin-2-ylindoles from 2-alkynylpyridines and 2-iodoanilines is described herein. The unexpectedly high regioselectivity can be rationalized by a combination of steric, coordinative and electronic effects.

The assembly of functionalized indoles, which are present in scores of natural products and pharmaceutical compounds,[1] has captured the attention of synthetic chemists, and is reflected by a large number of review articles.[2] Our interest in these compounds derived from the need to develop a short and cost-efficient route to 3-substituted-2-pyridin-2-ylindoles which have been identified as key synthetic intermediates in an ongoing program.

The regioselective construction of 2,3-disubstituted indoles remains challenging although lately several elegant approaches have been developed,[3] including the palladium-catalyzed reaction of *o*-haloanilines with internal alkynes,[4] which is known as the Larock indole annulation and appeared most appropriate for our purposes (Scheme 1).[5]

Mechanistically, this reaction involves oxidative addition of Pd(0) to the aryl halide, usually the iodide, to Pd(0), *syn*-insertion of the alkyne into the Ar–Pd bond, nitrogen displacement of the halide at Pd in the resulting vinyl-Pd intermediate, and finally reductive elimination of Pd(0).[4] The annulation has been described as regioselective with unsymmetrical alkynes generally attaching the aniline nitrogen moiety to the sterically more congested carbon atom of the alkyne, so that alkyne insertion occurs in a way to minimize steric strain in the vicinity of the developing carbon–carbon bond, which is shorter than the carbon–palladium bond.[4]



Scheme 1. Larock indole annulation with ethynylpyridines.

Early laboratory experiments demonstrated that the ratio of regioisomeric indole products was significantly

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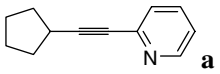
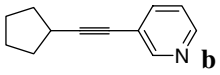
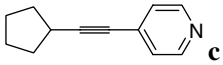
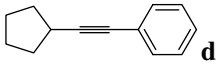
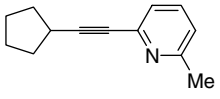
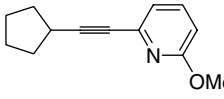
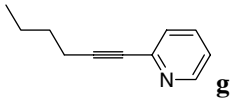
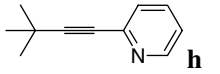
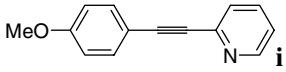
doi:10.1016/j.tetlet.2007.11.040

Table 1. Composition of product mixtures for the reaction **1**+**2**→**3**+**4**[a] versus steric parameters and pyridyl pK_a

Entry	Alkyne **2**	pK_a[11]	Molar ratio of **3**:**4**[b]	Yield **3**+**4**[c] (%)	*A*-value (ArR^3)/*A*-value (R^2)[12]
1	 **a**	2.77	94:6	94	2.97/1.67
2	 **b**	3.99	68:32	93	3.06/1.67
3	 **c**	4.98	72:28	76	2.99/1.67
4	 **d**	n/a	67:33	86	3.26/1.67
5	 **e**	3.49	87:13	88	3.19/1.67
6	 **f**	0.93	80:20	84	2.93/1.67
7	 **g**	2.67	97:3	91	2.97/1.54
8	 **h**	2.57	31:69	78	2.97/4.69
9	 **i**	1.76	41:59	56	2.97/3.24
10	 **j**	2.29	57:43	63	2.97/3.26

[a] All reactions were carried out on 1.5–3.0 mmol scale using 1.0 equiv 3-amino-4-iodobenzoic acid methyl ester **1a**, 1.5 equiv alkyne, 0.05 equiv $Pd(OAc)_2$, 0.075 equiv dppf, and 5.0 equiv KOAc in 50 vol NMP at 140 °C, and monitored by HPLC.[13]
[b] Determined by ^{1}H NMR integration.
[c] Isolated yield after column chromatography.

higher for 2-cyclopentylethynylpyridine (**2a**; Table 1, entry 1) than for cyclopentylethynylbenzene (**2d**, entry 4) and could therefore not be rationalized by steric differences between the acetylenic substituents. This intriguing observation, coupled with the absence of published studies describing the use of alkynylpyridines in Larock's indole annulation, prompted us to initiate a systematic investigation probing the influence of steric and electronic factors on the regioselectivity of the Larock indole annulation with selected alkynylpyridines.

We arrived at a suitable set of reaction conditions for the Larock reaction of a selected 2-iodoaniline **1**[6] and a 2-alkynylpyridine (**2**, X = N, Y = Z = CH; Scheme 1), optimized with respect to reaction rate, conversion, ratio of regioisomeric indoles **3** and **4** (with **3** being desired), and suppression of impurities derived from multiple alkyne insertion[7] and aniline dimerization.[8] It should be noted that while the palladium source and nature of the ligand affected the reaction rate considerably, they did not influence the regioselectivity. Therefore, all reactions were carried out using 1.5–3.0 mmol of aniline, 1.5 equiv of alkyne, 0.05 equiv of $Pd(OAc)_2$, 0.075 equiv of dppf and 5.0 equiv of KOAc in 50 mL of NMP per gram of aniline at 140 °C.

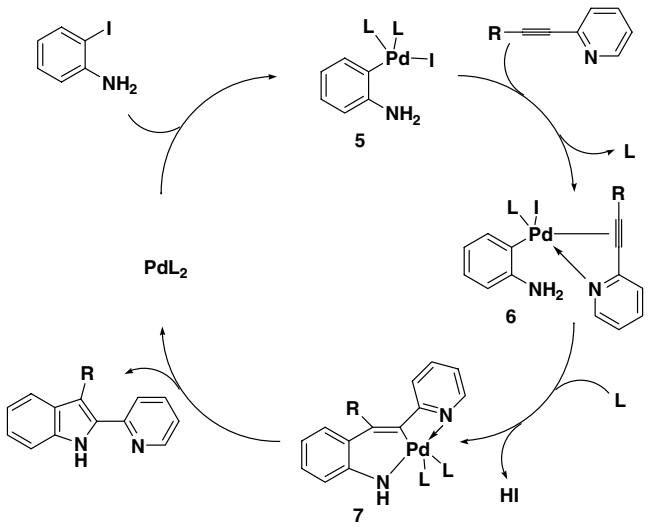
With these reactions conditions in hand, we embarked on the study of steric and electronic influences of alkynylpyridines on the regioselectivity of Larock's

indole annulation. Thus, 3-amino-4-iodobenzoic acid methyl ester (**1a**; $R^1 = CO_2Me$)[9] was reacted with disubstituted acetylenes **2a**–**j**, and the ratio and yield of the regioisomeric products **3** and **4** were determined (Table 1).[10] To qualitatively assess the influence of steric bulk of the acetylenic substituents, the *A*-values of these groups were determined by computational studies.[12]

Entries 1–4 provide results in accordance with Larock's observation in that the sterically bulkier acetylenic substituent favors its placement at C-2 of the resulting indole.[4] However, while acetylenes **2a**–**d** carry substituents with similar respective *A*-values, 2-cyclopentylethynylpyridine (**2a**) provided a significantly higher ratio of regioisomeric indoles **3** and **4** (94:6) compared to **2b**–**d** (ca. 69:31). It became apparent that the pyridin-2-yl moiety played an important role in this unexpected enhancement of regioselectivity favoring pyridin-2-yl-indoles **3**. This was further supported by entries 9 and 10, in which a ca. 50:50 ratio of indoles **3** and **4** would have been anticipated based on the *A*-values of the acetylenic substituents. These entries also suggest a role for mesomeric effects which needs to be studied further. However, the fact that sterics are still a significant component with respect to regioselectivity in the Larock indolization was supported by entry 8, as the large steric bulk of the *tert*-butyl group overrode the electronic effect of the pyridin-2-yl group favoring production of 3-pyridin-2-ylindole **4h** by 69 to 31. In general, however, introduction of the pyridin-2-yl substituent significantly favored 2-pyridin-2-ylindoles **3** over 3-pyridin-2-yl-indoles **4**. It became apparent that we were dealing with a complex overlap of steric and electronic effects.

Clearly, only 2-alkynylpyridines exhibit a behavior that deviates from a sterically-driven reaction. Their effect may be due to electronic effects (mesomeric or inductive) or to coordination of Pd by the pyridin-2-yl nitrogen lone pair at some point of the catalytic cycle. To probe the latter possibility, we examined the relationship of the pyridinyl pK_a of the alkynes with the observed regioselectivity. The calculated pK_a values[11] are shown in Table 1. Without the possibility of π-backbonding from the Pd to the pyridinyl moiety, a good correlation between σ-donicity and pK_a can be assumed.[14] In general, higher basicity at nitrogen, that is, increasing σ-donicity of the pyridinyl nitrogen towards palladium,[15] furnished enhanced regioselectivity in favor of 2-pyridin-2-yl indoles **3** (see entries 5 vs 6 and 10 vs 9). But this trend does not hold through the series (entry 1 vs 5), indicating that steric effects must play a role in the annulation with 2-cyclopentylethynyl-6-methylpyridine (**2e**), because the 2,6-disubstituted pyridines may have more difficulty in coordinating the Pd center. Since the pK_a effect goes against it, this particular steric effect must be considerable.

In an attempt to rationalize the role of the pyridin-2-yl substituent, the mechanism shown in Scheme 2 is postulated.[4] The pyridine moiety, which is known to act as a ligand for palladium, favors *syn*-insertion of the arylpalladium complex in a way to maintain coordination of palladium to the pyridyl nitrogen via a four-member ring (**6**→**7**). This coordination effect appears insignificant for pyridin-3-yl and pyridin-4-yl moieties.



Scheme 2. Proposed mechanism of Larock's indolization with 2-alkynylpyridines.

In summary, while steric effects are an important factor in governing the regiochemical outcome of Larock's indole annulation with 2-alkynylpyridines, the influence of the pyridin-2-yl nitrogen was also found to be significant and did correlate to some extent with its pK_a. The relative steric bulk and strong σ-donicity of the pyridin-2-yl moiety act in synergy to provide high regioselectivity favoring 2-pyridin-2-ylindoles **3** over 3-pyridin-2-ylindoles **4** observed in this study. This could render the Larock annulation to 2-pyridin-2-ylindoles an attractive synthetic protocol.

Experimental

Representative procedure for the Larock's indole annulation: To a 100 mL three-necked flask equipped with a magnetic stirrer, internal thermocouple, condenser and argon inlet, was added, at room temperature, the disubsituted alkyne (3.61 mmol), palladium(II) acetate (20.7 mg, 0.090 mmol), 1,1′-bis(diphenylphosphino)-ferrocene (75.8 mg, 0.135 mmol), potassium acetate (887 mg, 9.03 mmol), the 2-haloaniline (1.81 mmol), followed by anhydrous NMP (25 mL). The resulting dark mixture was heated at 140 °C until completion of reaction was determined by HPLC. Typically, the reactions completed within 1 h. The mixture was cooled to room temperature, filtered through a pad of Celite® which was rinsed with EtOAc (ca. 150 mL). Water (100 mL) was added and the two layers were separated. The aqueous phase was washed with EtOAc (1 × 100 mL). The organic layers were combined, washed with water, dried ($MgSO_4$) and concentrated to give generally a brown oil, which was purified by flash column chromatography (silica gel, 70–230 mesh, 60 Å) using hexane–EtOAc (10:1 to remove excess acetylene, then 5:1).

Acknowledgments

We thank Dr. Ruomei Li, Soraia Ahmadyar, Joseph Russell and Natasha Reddinger for technical support.

Supplementary data

Experimental procedures and characterizations for compounds **3a–j**, **4a–f** and **4h–j** are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.11.040.

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8. Dimerization of anilines **1** can occur via double Buchwald–Hartwig amination (a) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1348; (b) Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36*, 3609.
9. When 2-iodo-5-methoxyaniline (**1b**; $R^1 = OMe$) and 2-iodophenylamine (**1c**; $R^1 = H$) were annulated with 2-cyclopentylethynylpyridine (**2a**), the molar ratio of isomeric indoles **3** and **4** declined from 94:6, obtained with aniline **1a**, to 72:28 and 89:11, respectively. The reduced regioselectivity observed with anilines **1b** and **1c** versus **1a** may be the result of weaker coordination between the more electron-rich palladium and the pyridyl nitrogen of postulated complex **6** (Scheme 2).
10. The structural assignments were based on synthesis of authentic samples for **3a** and **3d** via cross-coupling reactions of 2-bromo-3-cyclopentyl-1-methyl-1*H*-indole-6-carboxylic acid methyl ester (Khodabocus, A.; Li, G.; Lu, Z.-H.; Roschangar, F.; Senanayake, C.H.; Shen, M. International Patent Application WO 2005092855, 2005) and NOE studies for **3/4b 3/4i** and **3/4j**.
11. The predicted pK_a values of the protonated pyridines at 25 °C and zero ionic strength in aqueous solutions were obtained using the ACD/I-Lab Web service (ACD/pK_a 8.02).
12. The theoretical *A*-values for each substituent were determined from the following equation: *A*-value = ΔH_f (axial) − ΔH_f (equatorial), where ΔH_f (axial) is the calculated heat of formation of the substituent in the axial position of a cyclohexane ring and ΔH_f (equatorial) is the calculated heat of formation of the substituent in the equatorial position of a cyclohexane ring. To ensure that the conformations studied were the lowest energy conformation of the system, a conformational analysis of the substituted cyclohexane ring, coupled with a torsional energy profile about the cyclohexyl-substituent bond (DFT, Jaguar v. 5.5, Schrödinger, LLC, Portland, Oregon, 2003), was performed for each substituent in its axial and equatorial position on a cyclohexyl ring. The ΔH_f (formation) values were calculated using MOPAC6 (AM1, geometry optimization, in Cerius2 v.4.9, Accelrys Inc., San Diego, CA, 2003).
13. Agilent 1100 HPLC system. Column: Agilent Zorbax Eclipse XDB-C8, 4.6 × 150 mm, 5 μm; P/N 935967-906. Mobile phase: A = water w/0.1% v/v trifluoroacetic acid (TFA), B = acetonitrile w/0.1% v/v TFA. Gradient Profile: 30–95% B over 14 min. UV detection @ 248 nm. 1.0 mL/min flow rate with injection volume of 5 μL.
14. It was demonstrated that the basicity, or the pK_a, of phosphines is related primarily to their σ-donicity, which is the ability of a ligand to donate σ-electrons to a transition metal, and to a lesser degree to the size of the ligand, and it was concluded that pK_a values are reasonable measures of the σ-donicity for those ligands that are pure σ-donor ligands and not π-acceptors Rahman, M. d. M.; Liu, H.-Y.; Eriks, K.; Prock, A.; Giering, W. P. *Organometallics* **1989**, *8*, 1.
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