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Synthesis of Novel Tetrahydroindeno[1,2-*b*]pyrrolidines via Ugi MCR and Palladium-Catalyzed Aerobic Oxidative Cyclization

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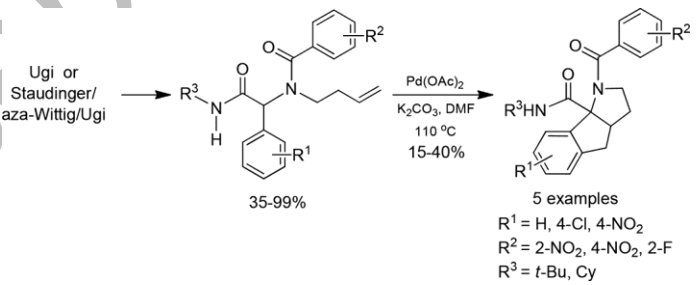
Abstract

Novel tetrahydroindeno[1,2-*b*]pyrrolidineswereconveniently prepared in moderate to good yields via a sequential Ugi multicomponent reaction or Staudinger/aza-Wittig/Ugi combination, followed by the palladium-catalyzed aerobic oxidative cyclization of the resulting Ugi adducts.



KEYWORDS: Tetrahydroindeno[1,2-b]pyrrolidines, Ugi reaction, oxidative cyclization.

INTRODUCTION

Synthetic Multi-Component Reactions (MCR´s) have emerged as an efficient and powerful tool in modern synthetic organic chemistry.[1] They are well known to be selective, efficient, atom economic, time and energy saving and easy to perform. MCR´s are extremely powerful to prepare structurally diverse complex molecules in a single chemical step and in combination with a second chemical transformation or post-condensation process ifimproves its chances to obtain more elaborated cyclic structures.[2–4] Among others MCRs, isocyanide-based MCRs (Ugi and Passerini) in combination with any intramolecular reaction, are the most used strategy to construct highly diverse heterocycles. Depending on the functional groups introduced during the MCR, several MCRs/post-condensation strategies have been described.[5–7]

Indeno[1,2-b]pyrrolidines are an interesting class of polycyclic heterocycles, which exhibit important biological effects. They have been reported to have hypoglycemic activity (**1**)[8] and recently, **2** has demonstrated high affinity and selectivity for the NMDA receptor.[9] To date, there are some synthetic methods for the preparation of tetrahydroindeno[1,2-b]pyrrolidines. In general they consist in multistep synthesis from unusual starting materials which incorporate one of two indeno[1,2-b]pyrrolidines cycles.[9,10–12] Recently, we have reported on palladium-catalyzed oxidative cyclization of *N*-arylpeptides which afforded some hydroindeno[1,2-b]pyrrolidines.[13] As an extension of this work we describe here the palladium-catalyzed oxidative cyclization of Ugi adducts to prepare new indeno[1,2-b]pyrrolidines which can be further transformed to more complex and constrained polyheterocyles.

RESULTS AND DISCUSSION

Ugi adducts**7a**-**g** were easily prepared in good yields (90-99%)by the reaction homoallylamine **3** with various aromatic aldehydes **4**, aromatic acids**5** and alkyl isocyanides **6**, in methanol with catalytic indium trichloride at room temperature.[14–17]

Compounds **7b**and **7e**-**h**were obtained via a Staudinger/aza-Wittig/Ugi[18] sequencefrom homoallyl bromide**8**. It is well documented that imines, the first Ugi intermediate, can be obtained from Staudinger iminophosphoranes and carbonyl compounds like benzaldehydes in good yields.[19]The Staudinger/aza-Wittig/Ugi combination has been used commonly to prepare Ugi derivatives from azides. In addition, the nucleophillic substitutionof sodium azide on alkyl halides is fully compatible with the Staudinger reaction in order to obtainany imine. Therefore, bromide was mixed with sodium azide in DMSO at 60 °C, and then were added successively PPh_3 and benzaldehydes**4**in order to get imine **9**. Assumingthe imine was formed,benzoic acid **5** and isocyanide **6**were added to the mixture to complete this route.Without further optimization, this combination affords the desired products in moderate yield (44-54%). In some cases the Passerini product **8**was obtained, which could explain the lower yields compared to original route (Ugi). Nevertheless, it turned out to be a general methodology to preparethe homoallyl Ugi derivatives from a cheaper and less volatile raw material than homoallyl amine.

Palladium cyclization was initially proved with compound **7e** using 5 mol% of palladium, 2 equivalents of K_2CO_3 and air as oxidant (Table 2, entry 1). Indeno[1,2-b]pyrrolidine **9e**

was recovered in 30% yield as single product and no starting material was detected.Comparing with the oxidative palladium cyclization of *N*-aryl amides (Ugi-Smiles), the *N*-acyl-amides (Ugi) gave lower yield. An attempt to improve this yield was performed by variations in the base and oxidant.However our initial conditions were the best in this process. Other bases such as 1,8-diazabicycloundec-7-ene (DBU) and NaH did not benefitthe reaction (Table 2, entry 2 and 3); the desired product **9e** was not detected. Some starting material was recovered in the case of DBU. When *p*-benzoquinone was used as the only oxidant the yield dropped to 10% and reaction time increased to 8 h (Table 2, entry 4). Finally, the yield using the combination of *p*-benzoquinone with oxygen (air) was slightly better than prior example but lower than only oxygen from air.[20]

With the best conditions in hand, oxidative palladium cyclization was performed with Ugi derivatives **7a**-**h** and six different indeno[1,2-b]pyrrolidines **9a**, **9b**, **9c**, **9e**, **9f** and **9h**were obtained. Higher-yield was achieved for compound **9f**. The presence of electron-withdrawing groups in both aromatic rings slightly enhances this cyclization process, where *p*-chloro derivatives **9c** and **9f** gave 5 to 10% more than corresponding benzene tetrahydroindeno[1,2-b]pyrrolidines**9b** and **9e**.It was not possible to evaluate the direct electron-donating effect of electron rich groups in both aromatics. However, the reaction did not proceeed with Ugi **7d**, which contains one methoxy group in *para* position at the nitro aromatic ring, indicating a negative effect.Finally, compounds **9g**were not found in crude reaction mixture.

This oxidative cyclizationprocess complements our mechanism proposed in 2007 (Figure 2), where the acidic proton removal in **7e** is associated withPd-enolate**I**creation and capture by the olefin to formPd-alkyl intermediate **II**which further cyclizes onto the aromatic ring. In agreement to our resultsthe Pd-enolate **I** is better stabilized by electron-withdrawing groups as nitro or chloro.[13]The higher yields observed with *N*-aryl amides (Ugi-Smiles) can be explained in the first step, where Pd-enolate **I** seems to be better stabilized by*p*-nitrophenyl group or it could be the *N*-acyl group destabilizes the enolate formation because of the complexation of Pd with a second carbonyl group. The use of benzoquinone as single oxidant is reported in similar palladium-catalyzed reactions.However, according to our results, the Pd (0) generated is oxidized back to Pd(II) more efficiently by air oxygen than benzoquinone.

CONCLUSIONS

In summary, we have prepared six new indeno[1,2-b]pyrrolidinesusing a two step Ugi/Palladium-Catalyzed Aerobic Oxidative Cyclizationin moderate yields. Electron-withdrawing groups are important to produce the oxidative palladium cyclization in *N*-acyl amides (Ugi). Further work is necessary to improve palladium oxidative process with this type of Ugi products. In addition,this method would be useful for rapid access to this new type of bioactive polyheterocycles.We believe this method hasa significant synthetic value due conformationally constrained*L*-proline derivatives can be prepared and therefore we are working to extend it.

EXPERIMENTAL

Typical Procedure For The Synthesis of Ugi Compounds

Acid (1 mmol) and isocyanide (1 mmol) were added successively to a mixture of homoallyl amine (1 mmol) and benzaldehyde (1 mmol)and 5% mol of $InCl_3$ in methanol (0.5 M). The resulting mixture was stirred at room temperature during 18 h before being concentrated under reduced pressure. The crude product was chromatographed using a mixture of hexane and ethyl acetate as the eluents, affording the pure Ugis **7a-f** in 90-99% yields.

***N*-(But-3-En-1-Yl)-*N*-(2-(*Tert*-Butylamino)-2-Oxo-1-Phenylethyl)-4-Nitrobenzamide (7e).**

A Colorless Viscous Liquid. ^{1}H NMR (400 Mhz, $Cdcl_3$)(δ, Ppm):8.22 (D, 1H, *J*=8.2 Hz, Ar-H), 7.73 (Dd, 1H, J_1=7.5 Hz, J_2=0.9 Hz, Ar-H), 7.61-7.52 (M, 2H, Ar-H), 7.45-7.36 (M, 5H, Ar-H), 6.06 (S_b, 1H, NH), 5.84 (S, 1H, CH-CO), 5.30-5.19 (M, 1H, CH=), 4.77-4.75 (D, *J*=9.9 Hz, 1H, CH_2=), 4.63-4.59 (D, 1H, *J*=17.1 Hz, CH_2=), 3.84-3.16 (M, 2H, CH_2), 2.42-1.97 (M, 1H, CH_2), 1.40 (S, 9H, CH_3-C). ^{13}C NMR (100 Mhz, $Cdcl_3$)(δ, Ppm): 168.5, 144.9, 135.0, 134.3, 133.9, 132.8, 130.1, 129.9, 129.8, 129.5, 129.1, 128.8, 128.5, 124.8, 116.8, 63.5, 51.7, 47.9, 33.2, 28.5. HRMS (FAB):Calculated For $C_{23}H_{27}N_3O_4$ 409.4781 $[M]^+$; Found 410.2079.

Typical Procedure For The Synthesis Of Palladium Catalyzed Oxidative Cyclization

To a 0.2 M solution of Ugi adduct (1 mmol) in DMF were added successively 2 equiv. of K_2CO_3 and 5% mol of Pd $(OAc)_2$. The resulting mixture was stirred at 110 °C for 3 h under constant airflow suministrated by a ballon full or air. The reaction mixture was

diluted with water, and extracted with AcOEt. Organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was chromatographed product was chromatographed using a mixture of hexane and ethyl acetate as the eluents, affording the pure indeno[1,2-b]pyrrolidine **9a-h** in 15-40% yields.

_N_-(_Tert_-Butyl)-1-(4-Nitrobenzoyl)-2,3,3a,4-Tetrahydroindeno[1,2-_B_]Pyrrole-8b(1_H_)-Carboxamide (9e).

A colorless viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$)(δ, ppm): 8.24 (dd, 2H, J_1=6.9 Hz, J_2=1.8 Hz), 8.12 (d, 1H, J_1=7.0 Hz), 7.67 (dd, 2H, J_1=7.0 Hz, J_2=1.9 Hz), 7.38-7.29 (m, 3H), 5.41 (s_b, 1H, NH), 3.70-3.63 (m, 1H), 3.47-3.41 (m, 1H), 3.27-3.17 (m, 2H), 2.84-8.80 (m, 1H), 2.29-2.22 (m, 1H), 1.71-1.62 (m, 1H), 1.29 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$)(δ, ppm): 170.5, 167.6, 148.2, 143.6, 143.4, 141.5, 129.7, 128.1, 127.9, 127.7, 125.9, 123.7, 82.1, 51.6, 51.3, 50.1, 35.1, 31.1, 28.6. HRMS (FAB):calculated for $C_{23}H_{25}N_3O_4$ 407.4623 $[M]^+$; found 408.1905.

Supporting Information

Full experimental detail, ^{1}H and ^{13}C NMR spectracan be found via the "Supplementary Content" section of this article's webpage.

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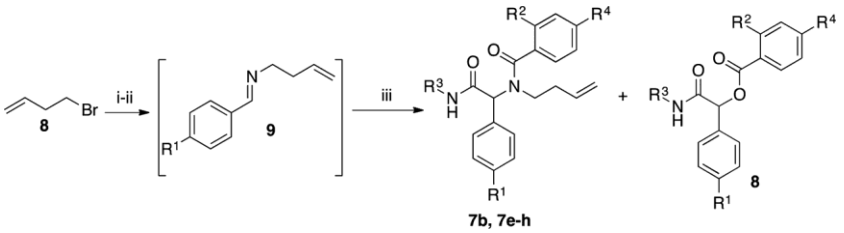
Table 1. Synthesis of Ugi adducts **7b** and **7e-h**via Staundinger/aza-Wittig/Ugi.[a]

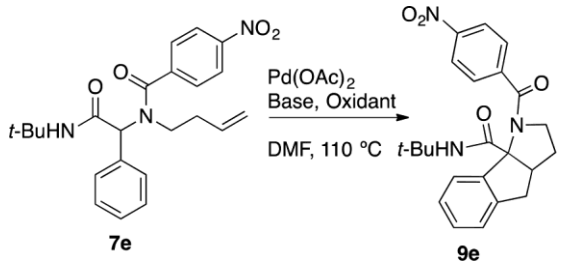


Entry	Product	R^1	R^2	R^3	R^4	Yield/%[b]	
						7	**8**
1	**b**	H	NO_2	*Tert*-Butyl	H	57	10
2	**e**	H	H	*Tert*-Butyl	NO_2	53	15
3	**f**	Cl	H	*Tert*-Butyl	NO_2	54	11
4	**h**	Cl	NO_2	Cyclohexyl	Cl	52	10

[a] Reaction conditions: i. NaN_3(1 mmol), DMSO (1 mL) 60 °C, ii. Benzaldehyde **4** (1 mmol)

and PPh_3 (1 mmol). iii. Benzoic acid **5** (1 mmol), Isocyanide **6** (1 mmol), MeOH (1 mL), 60 °C.

Table 2. Optimization of palladium-catalyzed oxidative cyclization.

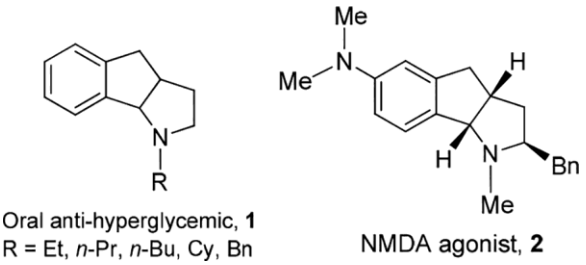


7e 9e

Entry	Base	Oxidant	Time/h	Yield/%
1	K_2CO_3	O_2 (Air)	4	30
2	DBU	O_2 (Air)	15	0
3	NaH	O_2 (Air)	3	0
4	K_2CO_3	*p*-benzoquinone[a]	8	10
5	K_2CO_3	O_2(air)/*p*-benzoquinone[a]	3	20

[a] Benzoquinone (2 mmol).

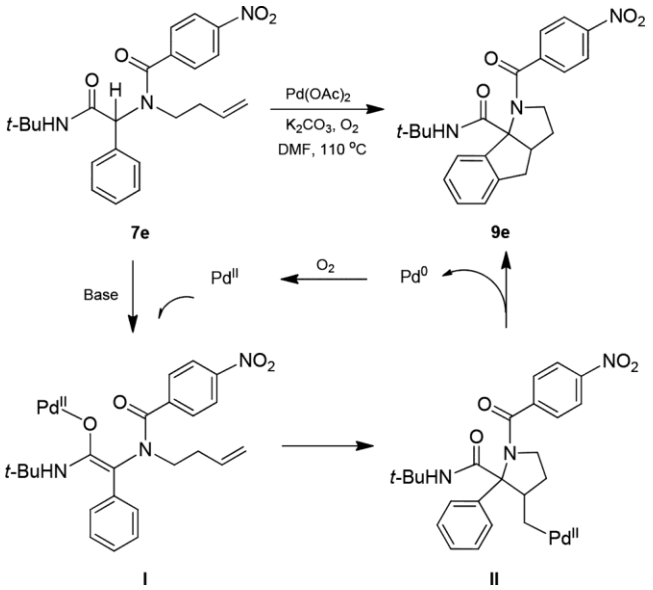
Figure 1. Bioactive Indeno[1,2-b]pyrrolidines



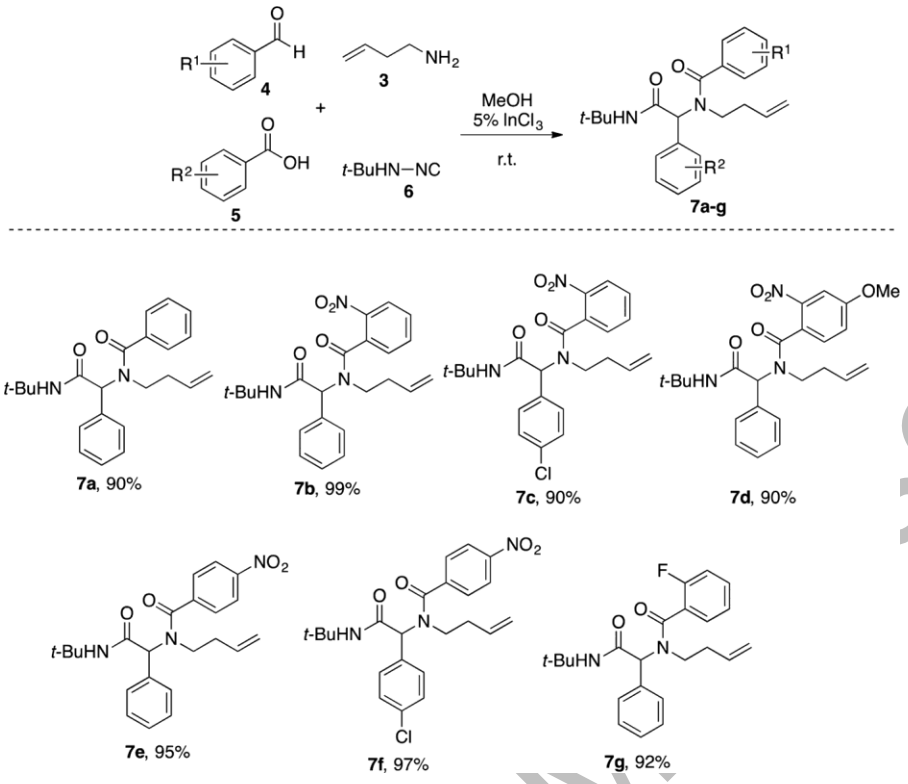
Oral anti-hyperglycemic, **1**
R = Et, *n*-Pr, *n*-Bu, Cy, Bn

NMDA agonist, **2**

Figure 2. Palladium-catalyzed oxidative cyclization-proposed mechanism.



Scheme 1. Synthesis of Ugi adducts **7a**-**7g**.



Scheme 2. Tetrahydroindeno[1,2-b]pyrrolidines **9a-c**, **9e-f** and **9h.**.