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Synthesis of Ring-Fused Oxazolo- and Pyrazoloisoquinolinones by a One-Pot Pd-Catalyzed Carboxamidation and Aldol-Type Condensation Cascade Process

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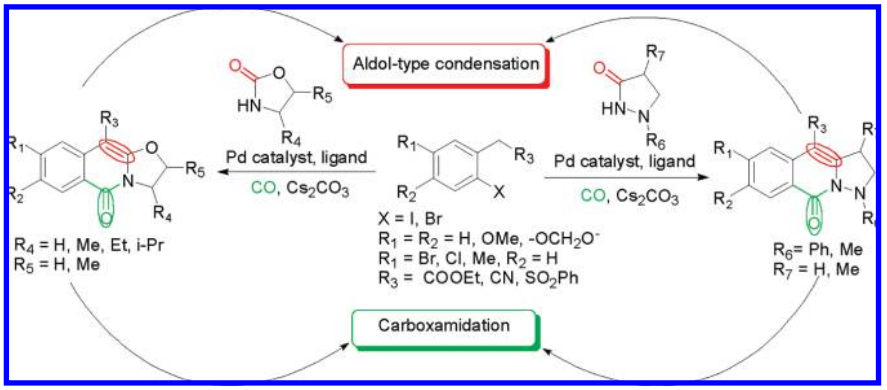

A three-component cascade process is described for the synthesis of ring-fused oxazolo- and pyrazoloisoquinolinones by a one-pot carboxamidation/aldol-type condensation reaction. The cascade process involves Pd-catalyzed carboxamidation of an aryl halide/active methylene compound with oxazolidinone or pyrazolidinone, and subsequent intramolecular base-catalyzed cyclization/dehydration through an aldol-type condensation process, to give ring-fused oxazolo- and pyrazoloisoquinolinones. This methodology provides an easy one-step approach to these important classes of nitrogen-containing heterocycles and can tolerate a wide array of functional groups, including ester, nitrile, methoxy, and halide.

Introduction

Nitrogen-containing heterocycles constitute a widespread structural motif in many biologically active molecules and natural products.[1] Among these, derivatives of isoquinolinone comprise an important class of heterocycles often encountered in alkaloids and other pharmacologically important compounds.[2] Ring-fused oxazoloisoquinolinones exhibiting diverse biological properties such as anti-inflammatory and analgesic activities have been described.[3] In addition, the pyrazoloisoquinolinone fragment found in natural products such as antibiotics of type APHEs1−4, produced by the *actinomycete Strepto verticilliam griseo carnim*, exhibited remarkable cytotoxic activity against several tumor cell lines of different origin.[4] In spite of the occurrence of these heterocycles in a significant number of

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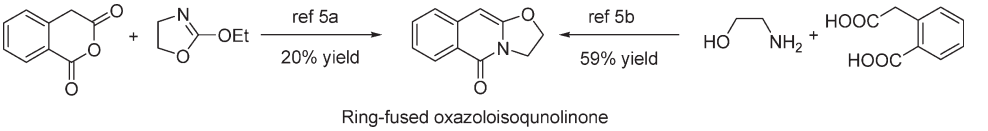
SCHEME 1

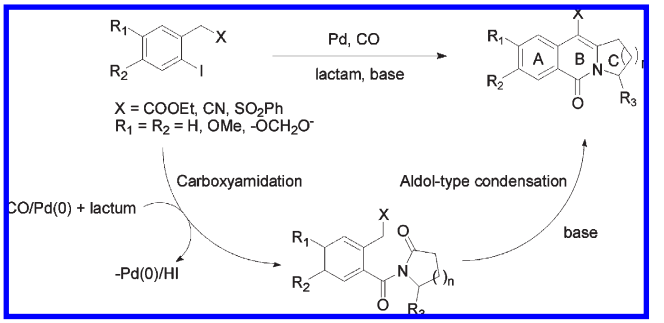


medicinal agents active toward a variety of diseases, there are very few synthetic methods described in the literature for the preparation of ring-fused oxazoloisoquinolinones. One approach is based on the condensation reaction of homophthalic anhydrides and homophthalic acids with cyclic imino ether and 2-amino ethanol, respectively.[3,5] These methods, however, typically provide moderate to low product yields (Scheme 1). Furthermore, to our knowledge, the synthesis of pyrazoloisoquinolinones has not yet been reported. Thus, we believe that the development of a facile approach to the synthesis of substituted ring-fused oxazolo- and pyrazoloisoquinolinone is a very worthwhile goal.

Classical organic synthesis usually involves the stepwise formation of individual bonds in the construction of a targeted molecule. However, the development of new methods for the simultaneous formation for example of both C−C and C−N (O) bonds in a single step is quite advantageous, since it allows the rapid buildup of molecular complexity from relatively simple starting materials.[6]

Transition metal-catalyzed reactions,[8] especially palladium-catalyzed carbonylative cyclization reactions for the formation of a wide variety of oxygen- and nitrogen-containing heterocycles, are a valuable synthetic tool for achieving this goal.[9−12]

SCHEME 2



In the context of our interest in the application of Pd-catalyzed cascade processes for the synthesis of heterocyclic compounds, we have recently described some new methods for the preparation of isoindolinones,[13] 2-carboxyindoles,[14] and substituted indocyclic enol lactones.[15] Specifically, we reported a novel cascade process for the synthesis of ring-fused substituted isoquinolinones using a three-component carboxamidation/aldol-type condensation cascade sequence from the corresponding aryl iodide/active methylene compound, carbon monoxide, and lactam in 60−95% yields (Scheme 2).[16]

In an effort to further diversify this cascade process, we evaluated the use of oxazolodinone and pyrazolidinone for the synthesis of the ring-fused oxazolo- and pyrazoloiso quinolinones (Scheme 3). This methodology provides high structural diversity in all three rings of the isoquinolinone skeleton.

Results and Discussion

Synthesis of Ring-Fused Substituted Oxazoloisoquinolinones. In our initial study in this area,[16] we found the optimized reaction conditions for this type of cascade process. Thus, the present reaction was first attempted by using 1 mmol of ethyl 2-(2-iodophenyl)acetate **1a** as the active methylene compound with the oxazolidinone **2a** (1.1 equiv)

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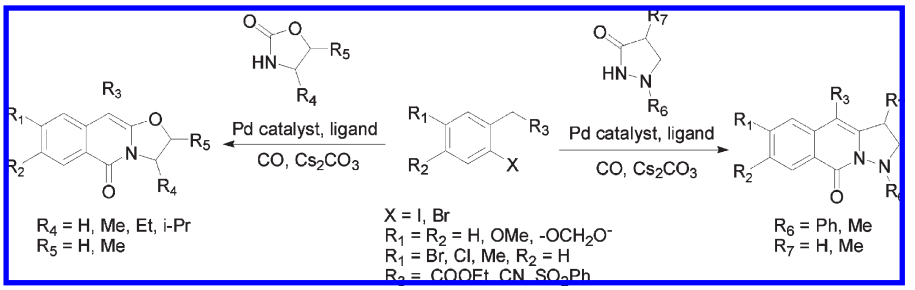
SCHEME 3



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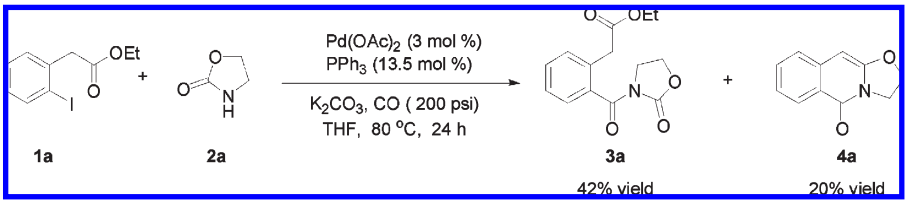

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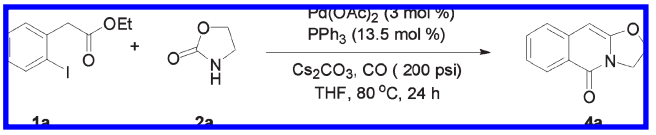

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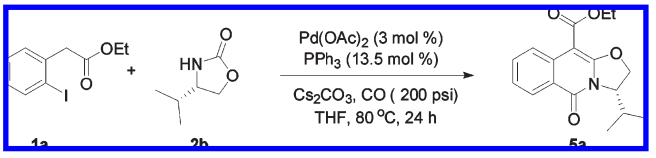

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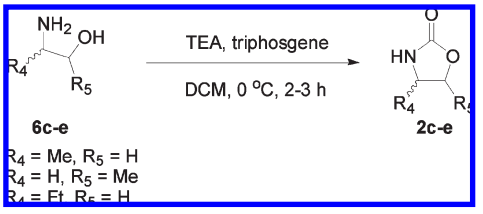


in the presence of 3 mol % of $Pd(OAc)_2$, 13.5 mol % of PPh_3, and 3.0 equiv of K_2CO_3 as a base in 6 mL of THF at 80 °C for 24 h under 200 psi of carbon monoxide. None of the expected cyclic product was formed, but we isolated two products from the reaction mixture, carboxamidated **3a** and decarboxylated **4a** in 42% and 20% yields, respectively (Scheme 4).

We then considered modifications to the reaction conditions, one of which involved change of the base from potassium carbonate to cesium carbonate. The use of Cs_2CO_3 afforded only the decarboxylated product **4a** in 40% isolated yield (Scheme 5).

Noting the importance of the base in this reaction, we decided to react an oxazolidinone containing a substituent α to the nitrogen atom, (*S*)-4-isopropyl-2-oxazolidinone **2b** with the active methylene compound **1a**. In this reaction no decarboxylation was observed, and the desired ring-fused substituted oxazoloisoquinolinone **5a** was obtained in 41% isolated yield (Scheme 6).

Since the formation of the desired ring-fused oxazoloisoquinolinone seemed to be dependent on the substitution of the oxazolidinone ring, we prepared various substituted oxazolodinones with a substituent located α to nitrogen and α to oxygen atoms to react under similar conditions. The synthesis of various alkyl-substituted oxazolidinones was accomplished by reaction of the corresponding amino alcohols (**6c**−**e**) with triphosgene in the presence of the base, TEA, as shown in Scheme 7.

We next investigated the reaction of ethyl 2-(2-iodophenyl)acetate **1a**, with (*R*)-4-methyloxazolidin-2-one **2c** in the presence of 3 mol % of $Pd(OAc)_2$ and 13.5 mol % of PPh_3 with 3 equiv of Cs_2CO_3 in THF (6 mL) at 80 °C for 24 h with 200 psi of CO. No acyclic product was detected and the ratio of the desired oxazolidinone **5b** to the undesired decarboxylated product **4b** was 86:14 (determind by GC and ^{1}H NMR analysis, Scheme 8).

Since the conversion of the active methylene compound **1a** to the desired ring-fused oxazolo-isoquinolinone was higher with (*R*)-4-methyloxazolidin-2-one **2c**, we decided to further optimize the reaction conditions by varying the nature and amount of the catalyst, reaction time, and CO pressure. The results are summarized in Table 1.

After some experimentation, we found that the cascade reaction could best be carried out by employing 1.5 mol % of $Pd(OAc)_2$ at 100 psi CO pressure for a reaction time of 4 h (Table 1, entry 3). The selectivity for the desired product **5b** decreased when the time was further reduced to 2 h (Table 1, entry 4). 1,3-Bis(diphenylphosphino)propane is a useful bidentate ligand for this transformation (Table 1, entry 5). The most active palladium catalyst for this cascade reaction is $PdCl_2(PPh_3)_2$, which afforded nearly complete conversion to the desired product **5b** (Table 1, entry 6). The reaction is sensitive to the nature of base, solvent, and the catalyst (Table 1, entries 7 and 8). Replacement of Cs_2CO_3 with K_2CO_3 gave poor conversion, while the use of different

SCHEME 8

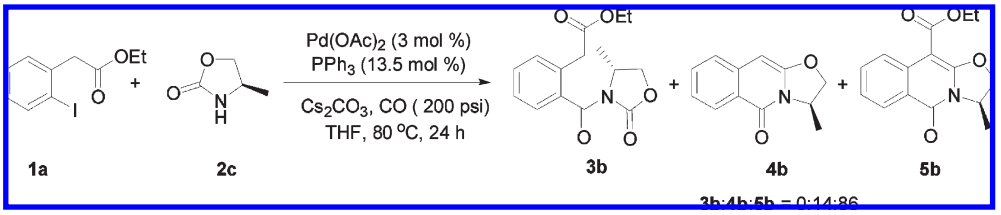
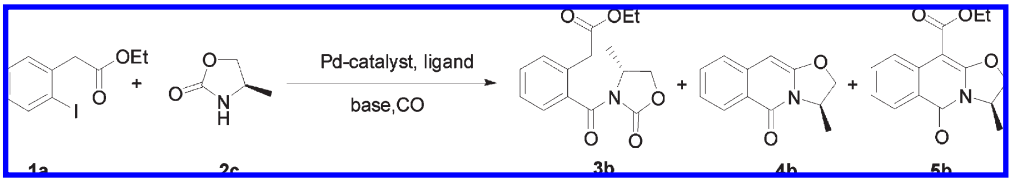


TABLE 1. Optimization of the Carboxamidation/Aldol-Type Condensation Cascade Reaction of Ethyl 2-(2-Iodophenyl)acetate 1a with (*R*)-4-Methyloxazolidin-2-one 2c[a]



entry	catalyst /phosphine (mol %)	CO (PSI)	base	solvent	time, h	ratio[b] **1a**/**3b**/**4b**/**5b**
1	$Pd(OAc)_2$ (3)/PPh_3 (12)	200	Cs_2CO_3	THF	15	−/−/14/86
2	$Pd(OAc)_2$ (1.5)/PPh_3 (6)	200	Cs_2CO_3	THF	7	−/−/14/86
3	$Pd(OAc)_2$ (1.5) /PPh_3 (6)	100	Cs_2CO_3	THF	4	−/−/15/85
4	$Pd(OAc)_2$ (1.5) /PPh_3 (6)	100	Cs_2CO_3	THF	2	-/13/14/73
5	$Pd(OAc)_2$ (1.5) /dppp (3)	100	Cs_2CO_3	THF	7	−/−/14/86
6	$PdCl_2(PPh_3)_2$(1.5)/PPh_3 (1.5)	100	Cs_2CO_3	THF	4	−/−/9/91
7	$PdCl_2(PPh_3)_2$ (1.5)/PPh_3 (1.5)	100	K_2CO_3	CH_3CN	24	14/39/18/29
8	$PdCl_2(PPh_3)_2$ (1.5)/PPh_3 (1.5)	100	K_2CO_3	THF	24	-/45/40/15
9	$PdCl_2$(*o*-tol)$_2$ (1.5)/P(*o*-tol)$_3$(1.5)	100	Cs_2CO_3	THF	4	4/−/20/76
10	$PdCl_2$(dppf)$_2$ (1.5)/dppf (1.5)	100	Cs_2CO_3	THF	4	−/−/18/82
11	$Pd_2(dba)_3$ (1.5)/ PPh_3 (4)	100	Cs_2CO_3	THF	4	−/−/19/81
12	$Pd(PPh)_4$ (1.5)	100	Cs_2CO_3	THF	4	−/−/15/85

[a]Reaction conditions: ethyl 2-(2-iodophenyl)acetate **1a** (1 mmol), (*R*)-4-methyl-oxazolidin-2-one **2c** (1.1 mmol), base (3 equiv), solvent (6 mL). [b]Ratio determined by ^{1}H NMR and by GC.

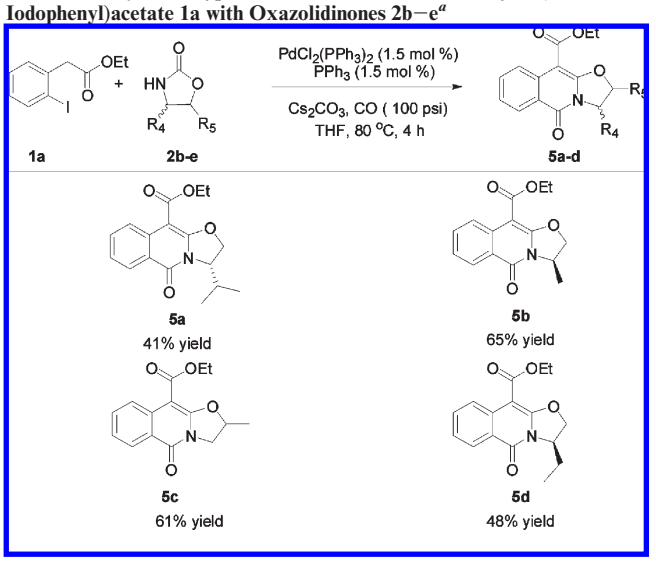
palladium catalysts and phosphine ligands such as $PdCl_2$(*o*-tol)$_2$/P(*o*-tol)$_3$, $PdCl_2$(dppf)$_2$/dppf, and $Pd_2(dba)_3$/PPh_3 provided reduced product ratios (Table 1, entries 9, 10, 11, and 12). Using the optimized reaction conditions we investigated the reaction of various substituted oxazolidinones with ethyl 2-(2-iodophenyl)acetate. The results are summarized in Table 2.

The reaction of ethyl 2-(2-iodophenyl)acetate **1a** with (*R*)-4-methyloxazolidin-2-one **2c** and 5-methyloxazolidin-2-one **2d** gave the desired products **5b** and **5c** in 65% and 61% yields, respectively. Similarly, good product yields were obtained with (*R*)-4-ethyl-oxazolidin-2-one **2e** (Table 2, products **5d**).

We also examined the reactivity of ethyl 2-(2-iodophenyl)-acetate bearing an electron-donating methoxy group. When ethyl 2-(2-iodo-4,5-dimethoxyphenyl)acetate **1b** was subjected to the cascade reaction under the optimized reaction conditions with (*R*)-4-methyloxazolidin-2-one **2c**, none of the desired product was formed, instead only the carboxamidated product **3c** was isolated in 61% yield (Scheme 9).

In an effort to obtain the desired product, we extended the reaction time and temperature (24 h, 110 °C) and also employed the strong base KO^{t}Bu. However, neither of these conditions provided ring-fused isoquinolinones and multiple products were detected on TLC because of the instability of oxazolidinones at higher temperatures and in the presence of a strong base. We also studied the reaction

TABLE 2. Synthesis of Ring-Fused Oxazoloisoquinolinones by Carboxamidation/Aldol-Type Condensation Cascade of Ethyl 2-(2-Iodophenyl)acetate 1a with Oxazolidinones 2b−e[a]



[a]Reaction conditions: ethyl 2-(2-iodophenyl)acetate **1a** (1 mmol), oxazolidinone **2b**−**e** (1.1 mmol), $PdCl_2(PPh_3)_2$ (1.5 mol %), PPh_3 (1.5 mol %), Cs_2CO_3 (3 equiv), CO (100 psi), THF (6 mL), 80 °C, 4 h .

of 3,4-methylenedioxy-6-iodophenylethyl acetate **1c** with (*R*)-4-methyloxazolidin-2-one **2c**, which afforded **5e** in 43% isolated yield (Scheme 9). It is noteworthy that when

SCHEME 9

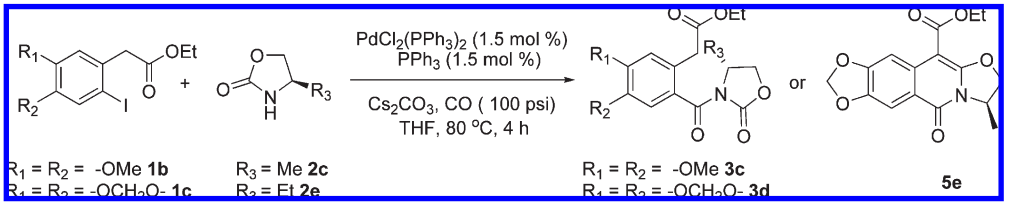
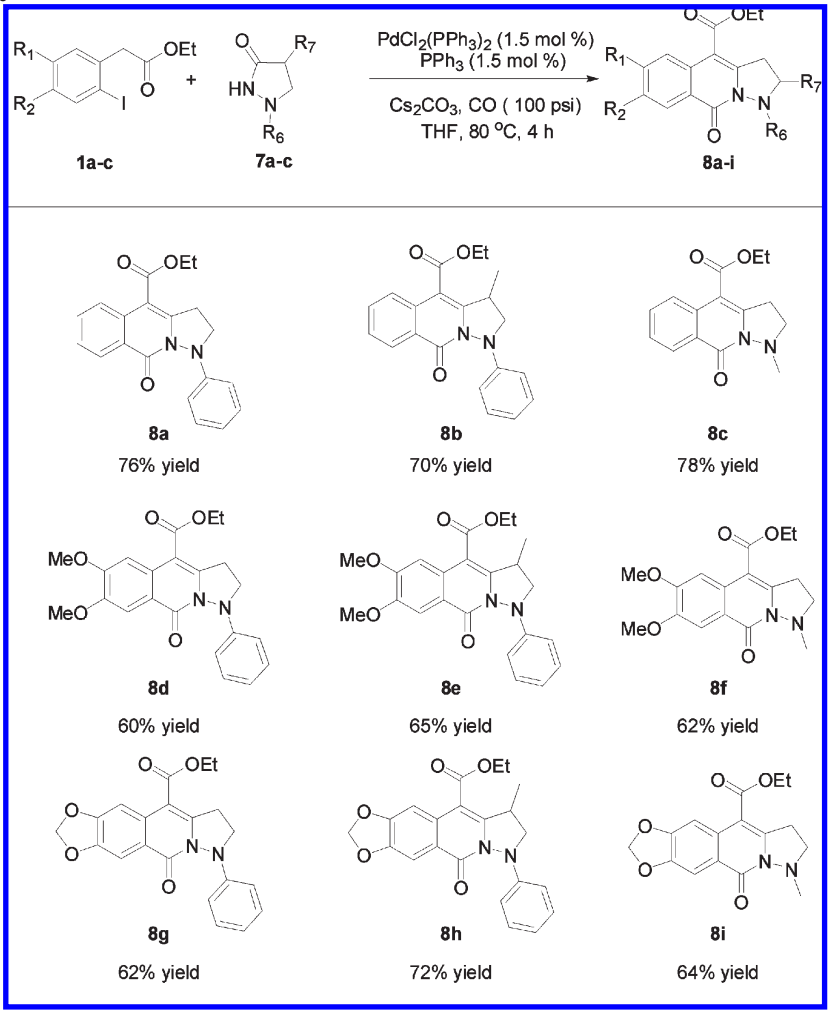


TABLE 3. Synthesis of Ring-Fused Pyrazoloisoqunolinones by Carboxamidation/Aldol-Type Condensation Cascade of Ethyl 2-(2-Iodophenyl)acetates 1a−c with Pyrazolidinones 7a−c[a]



[a]Reaction conditions: **1a−c** (1 mmol), **7a−c** (1.1 mmol), $PdCl_2(PPh_3)_2$ (1.5 mol %), PPh_3 (1.5 mol %), Cs_2CO_3 (3 equiv), CO (100 psi), THF (6 mL), 80 °C, 4 h.

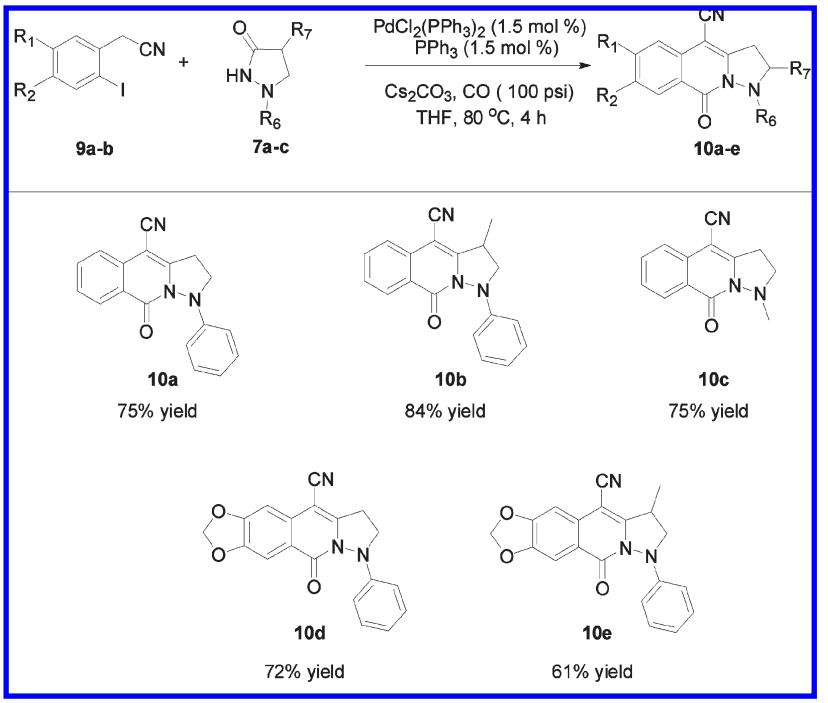
the reaction was carried out with 4-ethyloxazolidin-2-one **2e**, no cyclization was observed and only the carboxamidated product **3d** was isolated in 72% yield (Scheme 9).

Synthesis of Ring-Fused Substituted Pyrazoloisoquinolinones. In an effort to expand the scope of this cascade reaction, we investigated the reaction of various pyrazolidinones with different active methylene compounds to prepare ring-fused substituted pyrazoloisoquinolinones.

Reaction of Pyrazolidinones with Ethyl 2-(2-Iodophenyl)-acetates. In seeking access to ring-fused pyrazoloisoquinolinones, 1-phenylpyrazolidinone **7a** seemed an excellent cascade reactant with ethyl 2-(2-iodophenyl)acetate **1a**. When the latter (1 mmol) was reacted with 1-phenylpyrazolidinone (1.1 mmol), carbon monoxide (100 psi), $PdCl_2(PPh_3)_2$ (0.015 mmol), PPh_3 (0.015 mmol), and Cs_2CO_3(3 equiv) in dry THF (6 mL) at 80 °C for 4 h, the desired product **8a** was obtained in 76% isolated yield (Table 3).

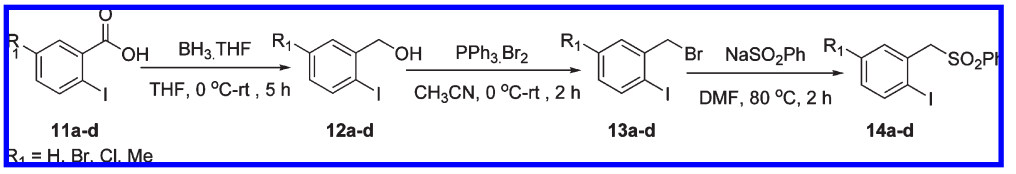
A variety of ethyl 2-(2-iodophenyl)acetates **1a−c** were reacted with different pyrazolidinones **7a−c** under the optimized reaction conditions, and the results are listed in Table 3. The cacade reaction of **1a** with 4-methyl-1-phenylpyrazolidin-3-one **7b** and 1-methylpyrazolidinone **7c** provided the corresponding ring-fused pyrazoloisoquinolinones in 70% and 78% isolated yields, respectively. We have also

TABLE 4. Synthesis of Ring-Fused Pyrazoloisoqunolinone by Carboxamidation/Aldol-Type Condensation of 2-Iodophenyl Acetonitriles 9a,b with Pyrazolidinones 7a−c[a]



[a]Reaction conditions: **9a**,**b** (1 mmol), **7a**−**c** (1.1 mmol), $PdCl_2(PPh_3)_2$ (1.5 mol %), PPh_3 (1.5 mol %), Cs_2CO_3 (3 equiv), CO (100 psi), THF (6 mL), 80 °C, 4 h.

SCHEME 10



studied the reaction of ethyl 2-(2-iodophenylethyl)acetate bearing electron-donating groups (**1b** and **1c**) with various pyrazolidinones **7a**−**c**. The cascade reaction of electron-rich substrates (**1b** and **1c**) with pyrazolidionones **7a**−**c** afforded the corresponding ring-fused pyrazoloisoquinolinones **8d**−**i** in 60−72% isolated yield.

Reaction of Pyrazolodinone with 2-Iodophenyl Acetonitriles. We also extended the reaction to active methylene compound bearing a nitrile group. When 2-iodophenyl acetonitrile **9a** was subjected to reaction with 1-phenyl pyrazolidinone **7a** under the usual conditions, the desired product was obtained in 75% isolated yield (Table 4).

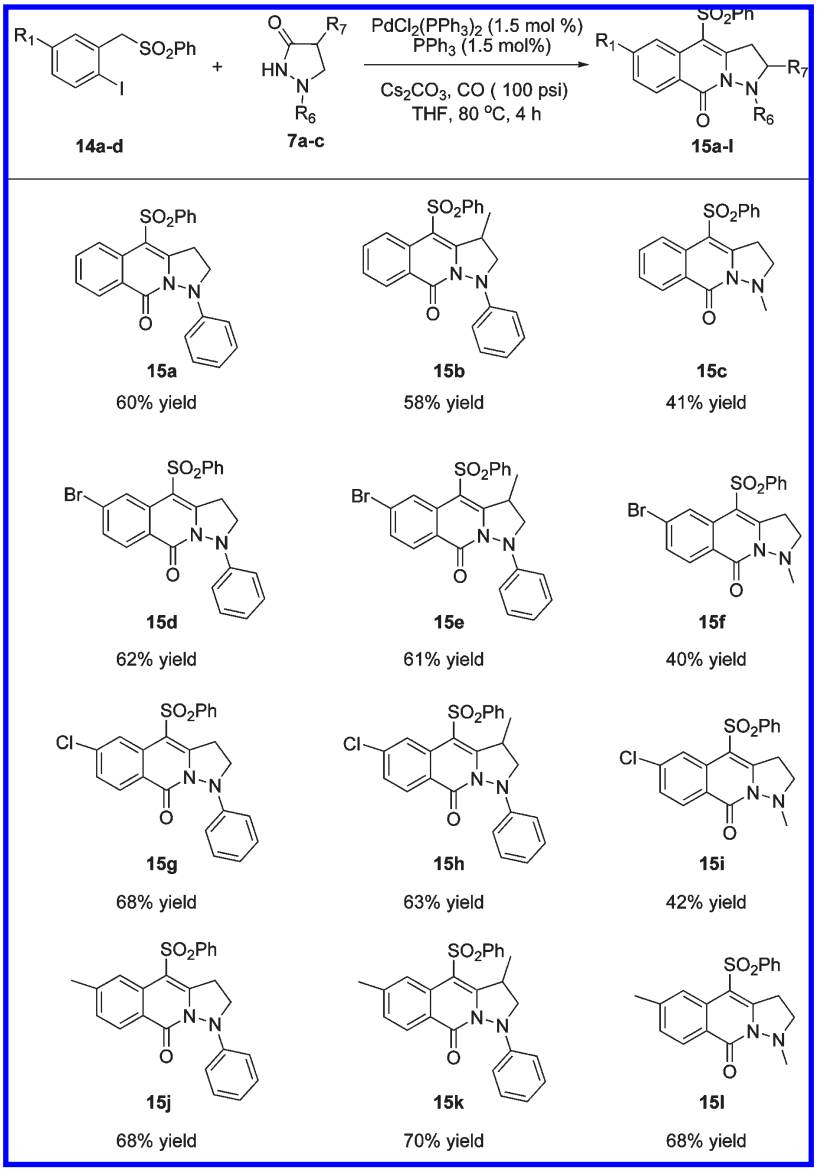
The cascade reaction of 2-iodophenyl acetonitrile **9a** with 4-methyl-1-phenylpyrazolidin-3-one **7b** and 1-methylpyrazolidinone **7c** provided the products in excellent yield (84% and 75%, respectively). The electron-rich (2-iodo-4, 5-dimethoxyphenyl)acetonitrile **9b** upon reacting with 1-phenylpyrazolidionone **7a** and 4-methyl-1-phenylpyrazolidin-3-one **7b** afforded corresponding ring-fused pyrazoloisoquinolinones in 72% and 61% yields, respectively.

Reaction of Pyrazolidinones with 2-Iodobenzyl Phenyl Sulfones. Various 2-iodobenzyl phenyl sulfones were prepared from the corresponding 2-iodophenyl acids in three steps in order to explore their reactivity for this type of cascade reaction (Scheme 10). Thus, 2-iodophenyl acids were reduced to their corresponding alcohols (**12a**−**d**) by using $BH_3 \cdot THF$.[17] Alcohols **12a**−**d** were then treated with $PPh_3 \cdot Br_2$ in DCM to form the corresponding benzyl bromides **13a**−**d** and the latter were subjected to reaction with $NaSO_2Ph$ in DMF at 80 °C for 2 h to give 2-iodobenzyl sulfones **14a**−**d** in 83−89% yields.

After preparation of the desired 2-iodobenzyl sulfones they were reacted with various pyrazolidinones **7a**−**c** to form the corresponding ring-fused pyrazoloisoquinolinones. The first substrate we tested was 2-iodobenzyl sulfone **14a**, which reacted with 1-phenyl pyrazolidinone **7a** to form pyrazoloisoquinolinone **15a** in 60% isolated yield (Table 5). On the other hand, reaction of **14a** with 4-methyl-1-phenylpyrazolidin-3-one **7b** and 1-methylpyrazolidinone **7c** provided pyrazoloisoquinolinones **15b** and **15c** in 58% and 41% isolated yield, respectively. We also examined the reactivity of 2-iodobenzyl sulfone bearing an electron-withdrawing bromo- and chloro-substituent. The electron-withdrawing groups had little influence on the product yields as the pyrazoloisoquinolinones **15d**−**i** were obtained in 40−68%

(17) Yoon, N. M.; Pak, C. S.; Brown Herbert, C.; Krishnamurthy, S.; Stocky, T. P. *J. Org. Chem.* **1973**, *38*, 2786.

TABLE 5. Synthesis of Ring-Fused Pyrazoloisoqunolinone by Carboxamidation/Aldol-Type Condensation of 2-Iodobenzyl Sulfones 14a−d with Pyrazolidinones 7a−c[a]



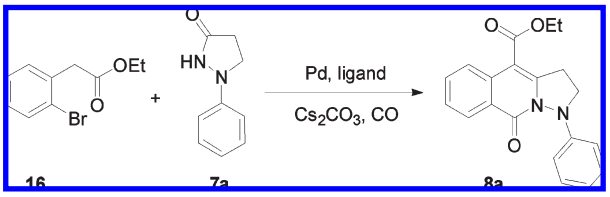
[a]Reaction conditions: **14a−d** (1 mmol), **7a−c** (1.1 mmol), $PdCl_2(PPh_3)_2$ (1.5 mol %), PPh_3 (1.5 mol %), Cs_2CO_3 (3 equiv), CO (100 psi), THF (6 mL), 80 °C, 4 h.

yields. However, the presence of an electron-donating methyl group afforded pyrazoloisoquinolinones **15j−*l*** in somewhat higher yields (68−70%).

Ring-Fused Pyrazoloisoquinolinones from 2-Bromo-Substituted Active Methylene Compounds. The cascade reaction sequence was next applied to 2-bromo-substituted active methylene compounds. Ethyl 2-(2-bomophenyl)acetate **16** was reacted with 1-phenylpyrazolidinone **7a** under the optimized reaction conditions; however, none of the desired product was obtained (Table 6, entry1). Increasing the reaction temperature or CO pressure or using toluene as a solvent also were unsuccessful (Table 6, entry 2), as was the use of bidentate phosphene ligands such as Xantphos and dppp with $Pd_2(dba)_3$ (Table 6, entries 3 and 4). The electron-rich phosphine PCy_3 afforded **8a** in 5% yield (Table 6, entry 5). After some experimentation, we found that this type of cascade transformation works well by employing $Pd_2(dba)_3$ as the Pd-catalyst (3 mol % Pd), $[HP^tBu_3][BF_4]$ as the ligand (12 mol %), and Cs_2CO_3 (3 equiv) as the base at 200 psi of CO pressure in toluene at 110 °C for 24 h to form pyrazoloisoquinolinone **8a** in 66% yield from 1-phenylpyrazolodinone (Table 6, entry 7).

Several 2-bromobenzyl sulfones were also used as substrates for the reaction. Treatment of 2-bromobenzyl sulfone **18** with 1-phenylpyrazolidinone **7a** provides the corresponding ring-fused pyrazoloisoquinolinone **15a** in 43% yield (Scheme 11). Similarly, 2-benzenesulfonylmethyl-1-bromonaphthalene **21**, which was prepared from 1-bromo-2-methylnaphthalene **19** in two steps, on reaction with 1-phenylpyrazolidinone **7a** and 4-methyl-1-phenylpyrazolidin-3-one **7b** afforded the corresponding ring-fused pyrazoloisoquinolinones **22a** and **22b** in 43% and 50% isolated yield, respectively (Scheme 12).

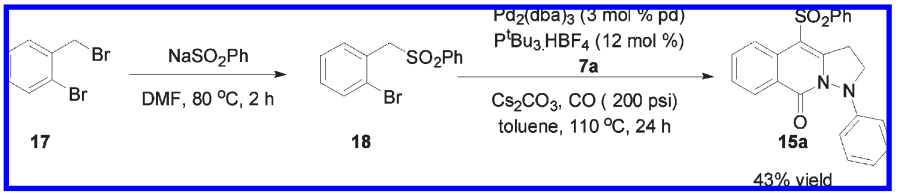
TABLE 6. Synthesis of Ring-Fused Pyrazoloisoquinolinone by Carboxamidation/Aldol-Type Condensation of Ethyl 2-(2-Bromophenyl)acetate 16 with Pyrazolidinones 7a[a]



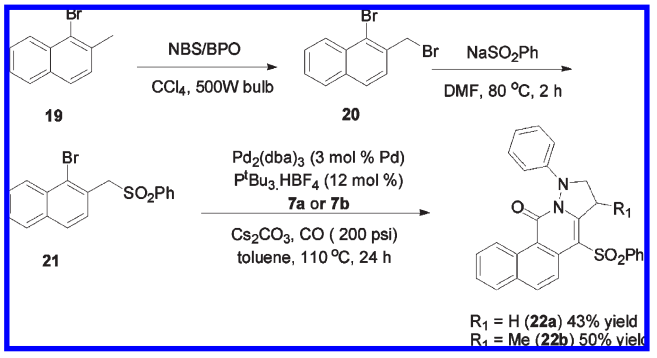
entry	Pd- catalyst (mol %)	ligand (mol %)	solvent	psi of CO	temp, °C	time, h	yield,[a] %
1	$PdCl_2(PPh_3)_2$ (1.5)	PPh_3 (1.5)	THF	100	80	24	0
2	$PdCl_2(PPh_3)_2$ (1.5)	PPh_3 (1.5)	toluene	200	110	24	0
3	$Pd_2(dba)_3$ (3)	Xantphos (6)	toluene	200	110	24	0
4	$Pd_2(dba)_3$ (3)	dppp (6)	toluene	200	110	24	0
5	$Pd_2(dba)_3$ (3)	$[HPCy_3][BF_4]$ (12)	toluene	200	80	24	5
6	$Pd_2(dba)_3$ (3)	$[HP^tBu_3][BF_4]$(12)	toluene	200	80	24	14
7	$Pd_2(dba)_3$ (3)	$[HP^tBu_3][BF_4]$(12)	toluene	200	110	24	66
8	$Pd_2(dba)_3$ (3)	$[HP^tBu_3][BF_4]$(12)	toluene	100	110	24	30

[a]Determine by ^{1}H NMR of crude.

SCHEME 11



SCHEME 12



Mechanism

A possible reaction mechanism for the formation of ring-fused oxazolo- and pyrazoloisoquinolinones is outlined in Figure 1. Oxidative addition of aryl halide/active methylene compound to the in situ generated palladium(0) species[18] leads to a palladium complex **23**. Insertion of carbon monoxide into the aryl carbon−palladium bond of **23** affords **24** and nucleophilic attack of the oxazolidinone or pyrazolidinone on an arylpalladium complex may give intermediate **25**. The latter can undergo reductive elimination affording carboxamide **26** with regeneration of palladium(0). The intramolecular condensation of the carbonyl group with benzylic anion **27** (generated by treatment with base) afforded intermediate **28**, which on dehydration gave the ring-fused oxazolo- and pyrazoloisoquinolinones.

(18) Macrind, R.; Ferguson, G.; Arsenault, G.; McAless, A. J.; Stephenson, D. K. *J. Chem. Res., Synop.* **1984**, 360.

Conclusion

In conclusion, we have developed a new route to ring-fused substituted oxazolo- and pyrazoloisoquinolinones via a three-component cascade process through one-pot carboxamidation/aldol-type condensation reaction sequences. A range of ring-fused oxazoloisoquinolinones and pyrazoloisoquinolinones were obtained from a variety of active methylene compounds. The products of these cascade reactions contain different functional groups that can be further functionalized and hence this methodology enables further molecular manipulation of these interesting nitrogen-containing heterocycles. Moreover, the strategy gives easy access to a variety of ring-substituted fused oxazolo- and pyrazoloisoquinolinones and thus could find wide applicability in pharmaceutical and medicinal research programs.

Experiment Section

General Procedure for the Palladium-Catalyzed Carboxyamidation/Aldol-Type Condensation Reaction of Aryl Halide/Active Methylene Compounds with Oxazolidinones and Pyrazolidinones. A glass liner containing a mixture of aryl halide active methylene compounds **1a**−**c**, **9a**,**b**, and **14a**−**d** (1 mmol), oxazolidinones **2b**−**e** or pyrazolidinones **7a**−**c** (1.1 mmol), catalyst $PdCl_2(PPh_3)_2$ (0.015 mmol), ligand PPh_3 (0.015 mmol), base Cs_2CO_3 (3 mmol), and THF (6 mL) was placed in a 45 mL autoclave equipped with a magnetic stirring bar. The autoclave was flushed three times with carbon monoxide and pressurized to 100 psi and heated at 80 °C for 4 h. The autoclave was removed from the oil bath and cooled to room temperature prior to the release of excess carbon monoxide. The reaction mixture was then filtered through a medium frit glass filter, rinsing with a minimal amount of reaction solvent, concentrated by rotary evaporation to yield the crude products; the latter was then

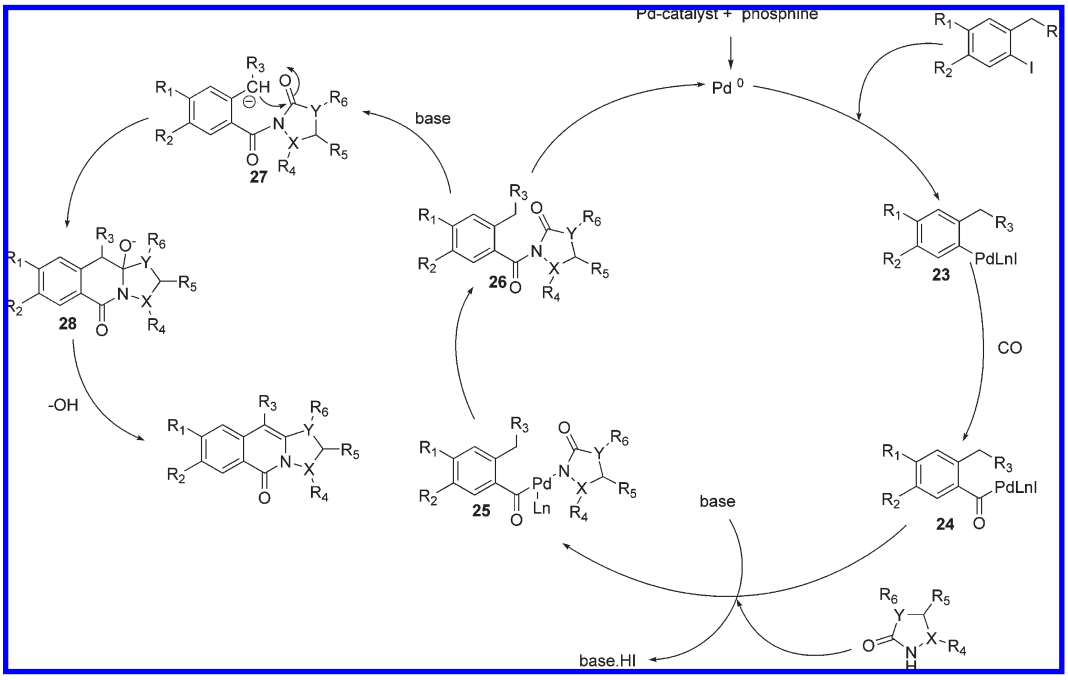


FIGURE 1. Proposed reaction mechanism for the formation of ring-fused oxazolo- and pyrazoloisoquinolinones.

purified by flash chromatography on silica gel with a mixture of ethyl acetate/hexanes as the eluant to afford **5a**−**e**, **8a**−**i**, **10a**−**e**, and **15a**−***l*** (products **10a**−**e** were recrystallized from acetone−dichloromethane).

General Procedure for the Palladium-Catalyzed Carboxyamidation/Aldol-Type Condensation Reaction of 2-Bromo-Substituted Active Methylene Compounds with Pyrazolidinones. A glass liner containing a mixture of aryl bromide/active methylene compounds **16**, **18**, and **21** (1 mmol), pyrazolidinones **7a**, **b** (1.1 mmol), catalyst $Pd_2(dba)_3$ (3 mol % Pd), ligand $[HP^tBu_3][BF_4]$ (12 mol %), base Cs_2CO_3 (3 mmol), and toluene (6 mL) was placed in a 45 mL autoclave equipped with a magnetic stirring bar. The autoclave was flushed three times with carbon monoxide, pressurized to 200 psi, and heated at 110 °C for 24 h. The autoclave was removed from the oil bath and cooled to room temperature prior to the release of excess carbon monoxide. The reaction mixture was then filtered through a medium frit glass filter, rinsing with a minimal amount of reaction solvent, concentrated by rotary evaporation to yield the crude products, which were purified by flash chromatography on silica gel with a mixture of ethyl acetate/hexanes as the eluant to afford **8a**, **15a**, and **22a**,**b**.

Acknowledgment. We are grateful to the Natural Sciences and Engineering Research Council of Canada for financial support of this research.

Supporting Information Available: Experimental procedures, characterization data for all new compounds, and copies of ^1H NMR and ^{13}C NMR spectra for substrates and products. This material is available free of charge via the Internet at http://pubs.acs.org.