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Study of Iridium Catalyzed N-Alkylation of Urea with Benzyl Alcohols

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Study of Iridium Catalyzed N-Alkylation of Urea with Benzyl Alcohols

A Thesis

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By

Majed Bajaber
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Dedicated to:

My mother, Latifah Bajaber

My wife, Huda Alsayed

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ABSTRACT

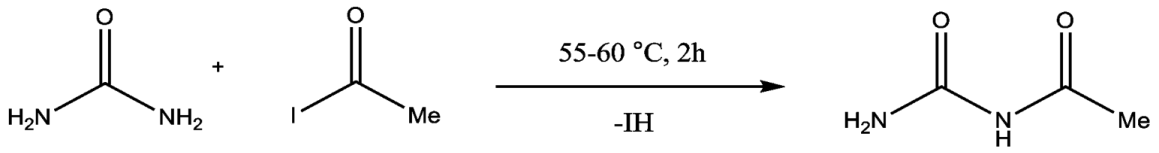
The solvent-free $(Cp^*IrCl_2)_2$ catalyzed N-alkylation of urea with benzyl alcohol has been studied. A variety of reaction conditions were studied and optimized to produce a high yield (82%) of N,N-dibenzylurea. A series of substituted benzyl alcohols were examined at the optimal reaction conditions. However, the preparation of substituted benzyl urea derivatives using conditions optimized for benzyl alcohol gave poor yields or intractable mixtures.

Keyword: chemistry; organic; urea; N-alkylation, iridium, benzyl alcohol.

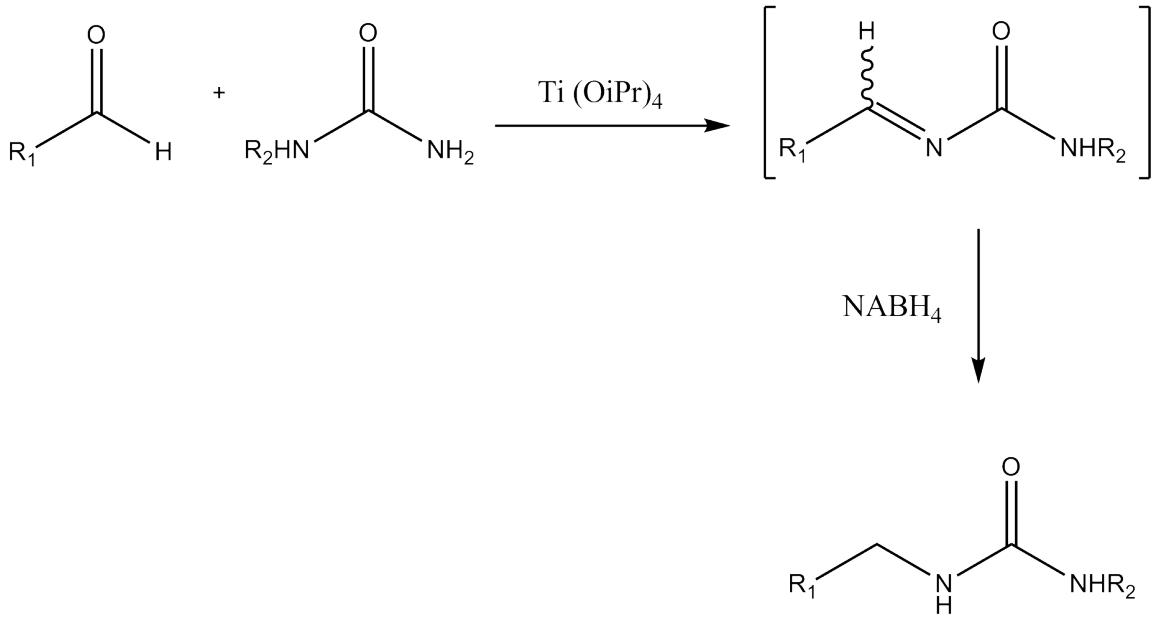
1. INTRODUCTION

1.1. Importance of Urea and N-Substituted Amides

Urea is an essential compound that plays an important role in most living organisms, in natural products, and in non-natural compounds. The synthesis of substituted ureas is widely used in organic chemistry due to its application in fine chemicals, medicine, and agriculture.[1,2] Furthermore, the N-substituted urea is an important functional group that serves as a protecting group for carboxylic acid derivatives and amines in synthetic chemistry.[3] Most of the synthetic methods of substituted ureas reported in the past have disadvantages such as using highly toxic isocyante or ecologically hazardous phosgene derivatives.[4] Similarly, N-alkylation with alkyl halides is a well-known method that has been utilized recently; however, this methodology is still undesirable due to the toxicity of most alkyl halides (Scheme 1).[5-7] Another technique for N-alkylation can be achieved by reductive amination of a ketone or aldehyde, but this route requires use of strong reducing reagents or hydrogen gas (Scheme 2). Therefore, the search for new methods for the N-alkylation of urea is highly desirable. [8-10]



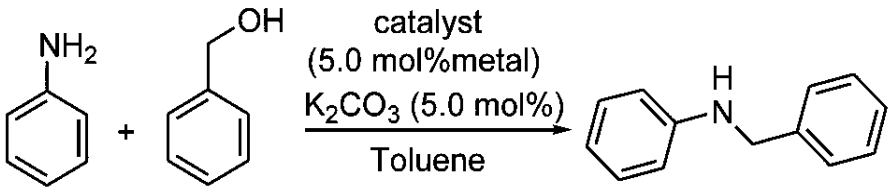
Scheme 1. N-Alkylation of urea by alkyl halides.



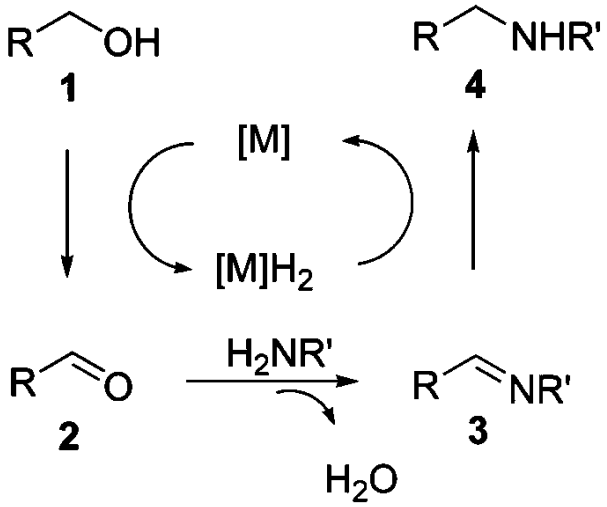
Scheme 2. N-Alkylation of urea by reductive amination.

1.2 Transition Metal Catalyzed N-Alkylation of Amines with Alcohols

Recently, transition metal catalysts (Ru, Ir) have been utilized to form C-N bonds by the reaction of amines with alcohols (Scheme 3).[11-13] The mechanism of the reaction is based on a hydrogen borrowing concept that generates water as a byproduct (Scheme 4).[14,15] It is an alternate method for the dehydrative coupling of amines with alcohol. The short-term removal of the hydrogen in the alcohol **1** converts it into the aldehyde **2** and forms a metal hydride ([M-H_2]). The imine **3** is then produced by condensing the electrophilic aldehyde with an amine forming water as by-product. Finally, the transition metal catalyst ([M-H_2]) returns the borrowed hydrogen to the imine to form the alkylated amine **4**. These types of reactions typically require high temperatures and long reaction times. In addition, a base additive seems to be necessary to facilitate the reaction.



Scheme 3. Catalyzed N-alkylation of aniline with benzyl alcohol.



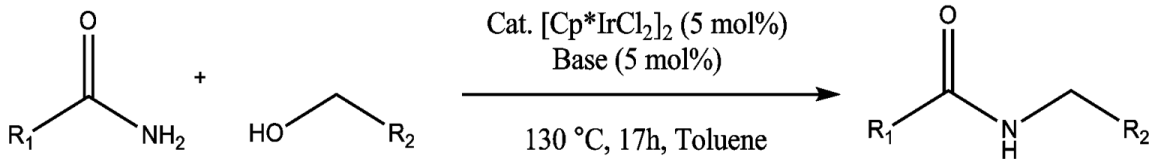
Scheme 4. Borrowing hydrogen strategy for the alkylation of amines with alcohols.

Fujita and coworkers also reported the use of $(Cp^*IrCl_2)_2$ for the preparation of cyclic amines via N-alkylation of primary amines by diols.[16] This methodology allowed for the synthesis of N-heterocyclic products without generation of harmful by-products (H_2O is only by-product) and thus is an attractive green chemistry process. Trudell and coworkers were the first to describe the application of the iridium catalyzed N-

heterocyclization reaction for the synthesis of nicotine–related compounds and the first total the synthesis of the alkaloid noranabasamine.[17] Further studies by Zhao and coworkers have shown that N-heterocyclization of simple amine/alcohols systems can proceed under solvent-free, base-free microwave-assisted conditions.[18]

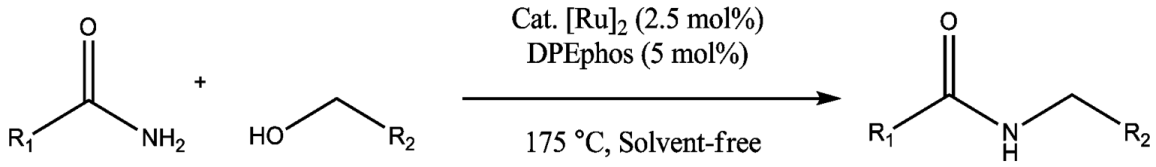
1.3. N-Alkylation of Amides

Fujita and coworkers reported the first N-alkylation of amides with alcohols by using 5 mol % of the iridium complex $[Cp^*IrCl_2]_2$.[19] This reaction involved refluxing toluene for 17h at 130 °C with 5 mol % of a base (Scheme 5). Later, Xu and coworkers reported that using transition metal catalysts such as Ir, Rh, and Ru in solvent-free conditions was successful for N-alkylation of amides with primary alcohols.[20] This reaction required a high temperature of 175 °C and a long reaction time of 35 hours (Scheme 6).



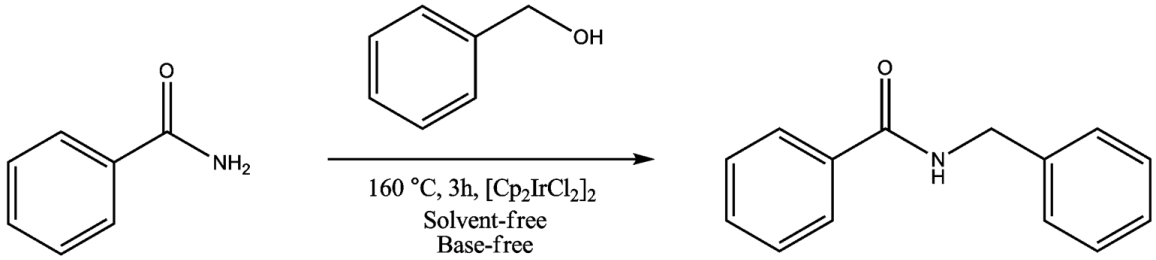
Scheme 5. N-Alkylation of primary amides with primary alcohol using iridium catalysis.

Based upon the success of the iridium-based catalytic system for the formation of C-N bonds with amines and amides by Fujita, Trudell and coworkers explored the potential application of iridium catalyzed N-alkylation of amides using solvent-free systems.

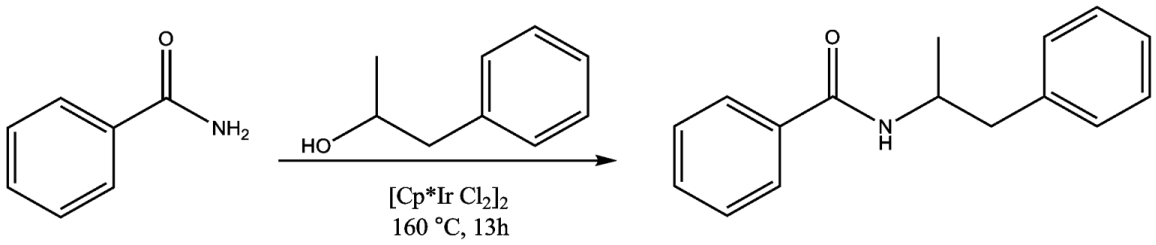


Scheme 6. Solvent-free, N-alkylation of primary amide with primary alcohol using ruthenium catalyst.

Subsequently, Trudell and coworkers reported the first solvent-free, base-free iridium catalyzed N-alkylation of amides with alcohols (Scheme 7).[21] In addition, these studies revealed that the reaction was not limited to primary alcohols and that secondary alcohols gave high yields of alkylation products. (Scheme 8).



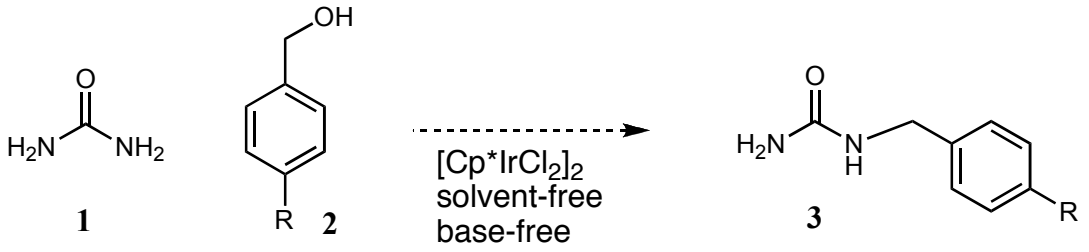
Scheme 7. Solvent-free, base-free iridium catalyzed N-alkylation of amides with benzyl alcohol.



Scheme 8. Solvent-free, base-free iridium catalyzed N-alkylation of amides with secondary alcohol.

2. RESULT AND DISCUSSION

The need for the development of new methods for the preparation of substituted urea derivatives prompted an investigation to evaluate the potential utility of the iridium catalyzed N-alkylation reaction. The goal of this investigation was to develop reactions conditions using $(Cp^*IrCl_2)_2$ that would exhibit wide substrate tolerance, exploit solvent-free, base-free mediated conditions and furnish novel substituted ureas (Scheme 9).

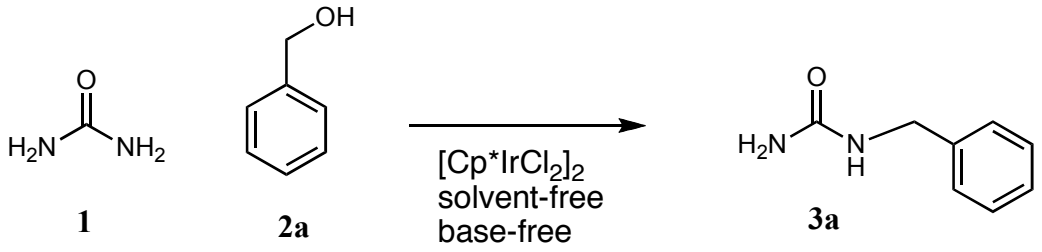


Scheme 9. Iridium catalyzed N-alkylation of urea with benzyl alcohol.

2.1. Solvent-free, Base-free Conditions

Initially, we investigated conditions for the N-alkylation of urea (**1**) with benzyl alcohol (**2**) in solvent-free, base-free conditions with 5 mol % of the iridium catalyst for 17 hours at a variety of different temperatures. It was found that under these conditions the urea did not react with benzyl alcohol using solvent-free, base-free conditions with one equivalent of benzyl alcohol (Table 1, Entries 1-3) despite the elevated temperatures. Only a nearly quantitative recovery of benzyl alcohol was observed. Subsequently, we examined the increase in the amount of benzyl alcohol up to three equivalents; however, the reaction offered no noticeable formation of product (Table 1, Entries 4-5).

Table 1. Solvent-free, base-free condition for N-alkylation of urea with benzyl alcohol.



1 2a 3a

Entry	1 (equiv)	2a (equiv)	$(Cp^*IrCl_2)_2$ (mol %)	T (°C)	3a, Yield [%]
1	1	1	5	120	NR
2	1	1	5	140	NR
3	1	1	5	160	NR
4	1	2	5	160	NR
5	1	3	5	160	NR

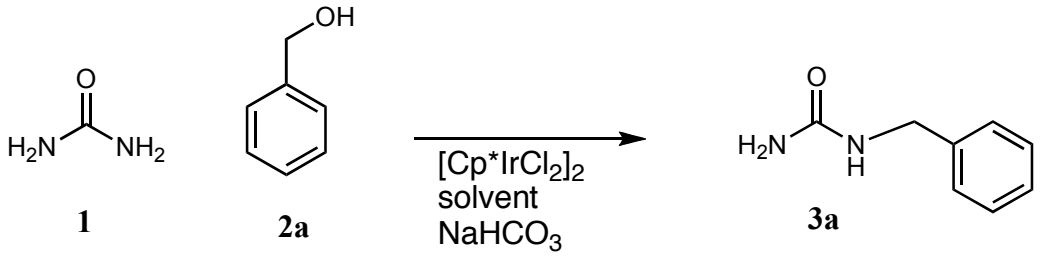
NR: no reaction, only starting material recovered.

2.2. Solvent and Base Effects

In order to find the optimum conditions for the N-alkylation of urea we investigated the use of various solvents and bases . Using 5 mol % of the iridium catalyst for 17 hours in presence of sodium bicarbonate, toluene, xylene, hexane and water were explored as solvents. We found that the solvent did not have a positive effect on the reaction (Table 2) and no N-alkylation was observed. Even when the amount of benzyl

alcohol was increased to three equivalents in toluene, no N-alkylation of urea was observed (Table 2, Entry 6).

Table 2. Solvents used for N-alkylation of urea with benzyl alcohol.



1 **2a** **3a**

Entry	1 (equiv)	2a (equiv)	Solvent (vol)	Base	$(Cp^*IrCl_2)_2$ (mol %)	T (°C)	Yield [%]
1	1	1	toluene (5 ml)	$NaHCO_3$	5	160	NR
2	1	1	xylene (5 ml)	$NaHCO_3$	5	160	NR
3	1	1	hexane (5 ml)	$NaHCO_3$	5	160	NR
4	1	1	water (3 mL)	$NaHCO_3$	5	160	NR
5	1	2	toluene (5 ml)	$NaHCO_3$	5	160	NR
6	1	3	toluene (5 ml)	$NaHCO_3$	5	160	NR

NR: no reaction, only starting material recovered.

The results of our previous studies using solvent-free conditions with different bases prompted us to investigate various bases to promote formation of an alkylation product.[21] We examined a variety of bases in multiple solvents (Table 3). As a result, we initially isolated N,N-dibenzylurea (**4**) in trace amounts using a strong base such as

potassium *tert*-butoxide in toluene (Table 3, Entry 4). Afterwards, we increased the benzyl alcohol to three equivalents and the N,N-dibenzylurea **4a** was furnished in <10 % yield (Table 3, Entry 6). Although we were surprised that the major product was the dibenzyl derivative and not the mono-benzylurea **3a**, we were encouraged by the result that some N-alkylation had occurred.

The formation of the N,N-dibenzylurea offers some insight to the reactivity of urea in this system. The fact that the N,N-dibenzylurea was the major product suggests that the intermediate N-benzylurea is more reactive than urea itself. Presumably, the N-benzyl group increases the nucleophilicity of the alkylated nitrogen atom due increased electron-donation from the benzyl group. As more benzaldehyde is produced by the catalytic cycle, subsequent reactions then take place at the N-benzylated nitrogen atom over reaction with urea or the unsubtituted nitrogen of N-benzylurea. Thus, N-benzylurea does not form again until all of the existing N-benzylurea has been consumed. As a result, N,N-dibenzyl urea (**4a**) is formed over N-benzylurea (**3a**) and N,N'-dibenzylurea (**5**).

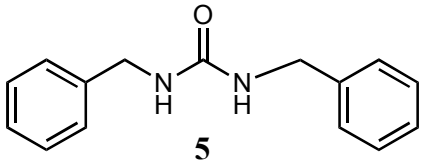


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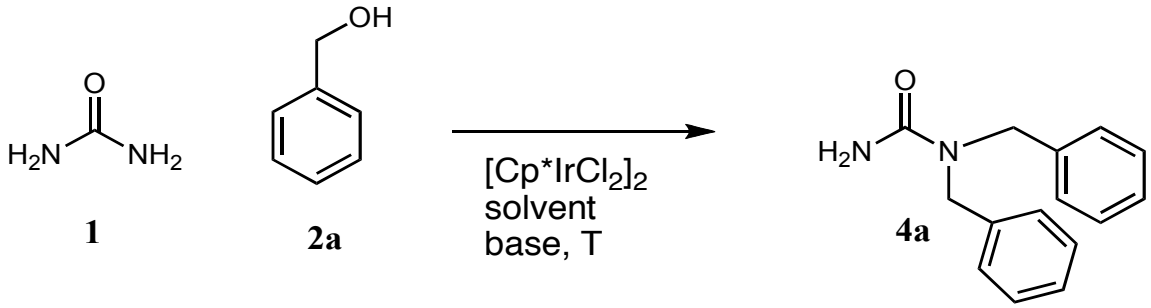
Table 3. Base and solvent conditions for N,N-dialkylation of urea with benzyl alcohol.



1 **2a** **4a**

Entry	1 (equiv)	2a (equiv)	Solvent (vol)	Base	$(Cp^*IrCl_2)_2$ (mol %)	T (°C)	Yield [%]
1	1	1	toluene (5 ml)	NaOH	5	160	NR
2	1	1	toluene (5 ml)	KOH	5	160	NR
3	1	1	water (3 ml)	KOt-Bu	5	160	NR
4	1	1	toluene (5 ml)	KOt-Bu	5	160	trace
5	1	2	toluene (5 ml)	KOt-Bu	5	160	<10
6	1	3	toluene (5 ml)	KOt-Bu	5	160	<10

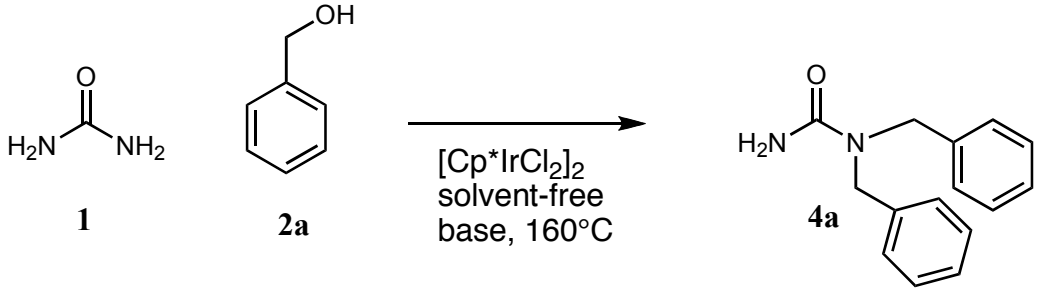
NR: no reaction, only starting material recovered.

2.3. Solvent-free Conditions for N,N-Dialkylation of Urea

The previous results encouraged us to investigate a variety of bases in solvent-free systems to develop reliable conditions for the N,N-dialkylation of urea. Thus, we carried out the reaction of urea with three equivalents of benzyl alcohol with 5 mol % of the iridium catalyst at 160 °C for 17 hours with different bases. As a result, we found that the

base played a key role in N,N-alkylation of urea with benzyl alcohol. It appears that good solubility of the base in benzyl alcohol favors increased yields of the alkylation product. The inorganic bases (NaOH and $NaHCO_3$, Table 4, entries 1-2) exhibited modest solubility and gave poor yields. However, the organic bases (KO-t-Bu and NaOAc, Table 4, entries 3-4) were easily dissolved and furnished detectable amounts of the N,N-dibenzylurea.

Table 4. Effect of base in solvent-free conditions for N,N-alkylation of urea with benzyl alcohol.



1 **2a** **4a**

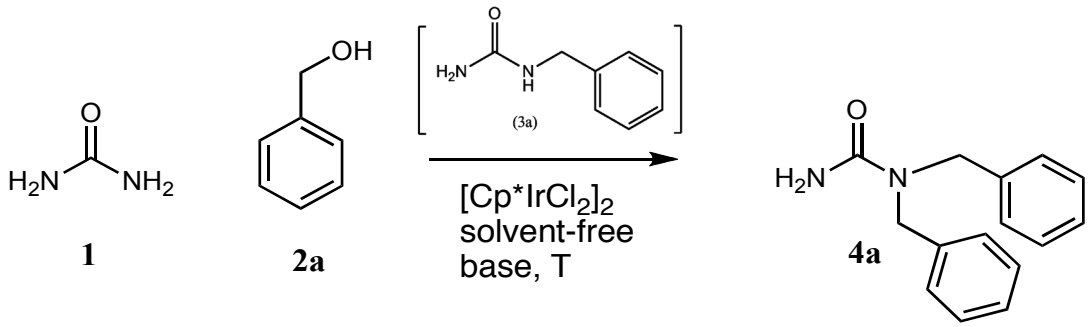
Entry	**1** (equiv)	**2a** (equiv)	Base	$(Cp^*IrCl_2)_2$ (mol %)	T (°C)	Yield [%]
1	1	3	NaOH	5	160	-
2	1	3	$NaHCO_3$	5	160	trace
3	1	3	KOt-Bu	5	160	<10
4	1	3	NaOAc	5	160	<20

2.4. Optimized Conditions

Serendipitously, it was discovered that a decrease in reaction temperature resulted in an improvement of the yield of N,N-dibenzylurea **4** (Table 5). The optimum reaction

temperature when using potassium *tert*-butoxide as a base was 120 °C. This afforded the N,N-dibenzylurea in 35% isolated yield. (Table 5, Entry 4). Furthermore, under these reaction conditions N-benzyl urea (**3a**) was detected as a product in trace amounts. In addition, we found that the use of sodium acetate showed an enormous improvement of yield of (**4a)** (82% isolated yield of N,N-dibenzylurea) at the lower reaction temperature of 120 °C (Table 5, Entry 9), while increasing the reaction temperature diminished the yield and formed an intractable mixture of other substituted urea derivatives (Table 5, Entry 3).

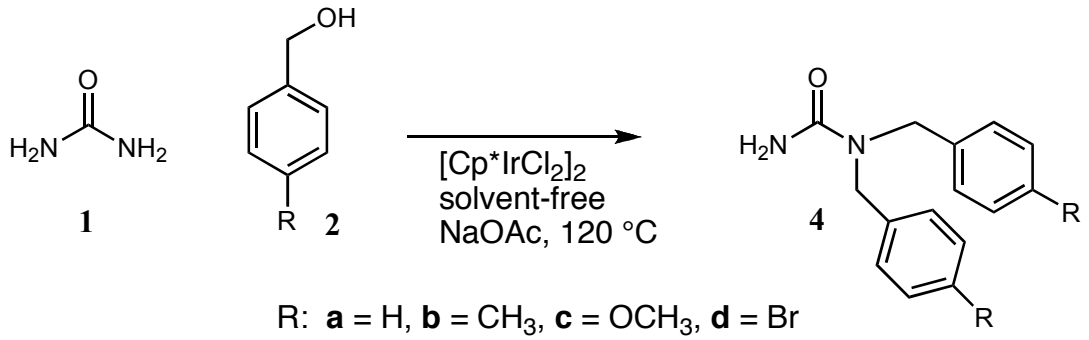
Table 5. Iridium catalyzed N-alkylation of urea with benzyl alcohol at lower temperature.



Entry	**1** (equiv)	**2a** (equiv)	Base	$(Cp^*IrCl_2)_2$ (mol %)	T (°C)	**4a** Yield [%]	**3a** Yield [%]
1	1	3	KOt-Bu	5	150	10	-
2	1	3	KOt-Bu	5	140	13	-
3	1	3	KOt-Bu	5	130	21	-
4	1	3	KOt-Bu	5	120	35	trace
5	1	3	KOt-Bu	5	110	19	trace
6	1	3	KOt-Bu	5	100	18	trace
7	1	3	KOt-Bu	5	90	16	trace
8	1	3	KOt-Bu	5	80	<10	-
9	1	3	NaOAc	5	120	82	<10
10	1	3	NaOAc	5	140	31	trace
11	1	3	NaOAc	5	160	<20	-

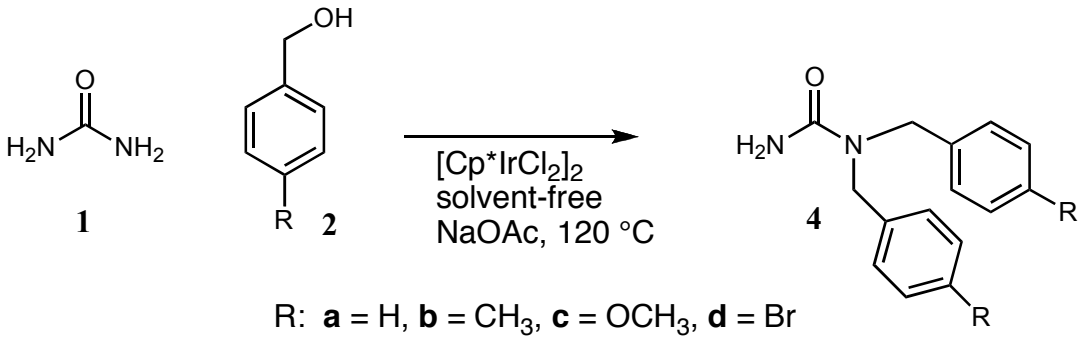
2.5. Examination of Scope and Limitations of the Optimized Conditions

Having optimized the conditions for N,N-dialkylation of urea with benzyl alcohol, we investigated substituted benzyl alcohols with electron-donating and electron-withdrawing groups (Scheme 10). The results showed that substitution on the aryl ring of benzyl alcohol greatly diminished the yield of the N,N-dibenzylurea derivative **4**. The presence of a modest electron-donating group in 4-methylbenzyl alcohol (**2b**), (Table 6, Entry 2) furnished the N,N-di(4-methyl)benzyl urea **4b** in less than 10% yield. The strong electron-donating 4-methoxy benzyl alcohol **2c** gave an intractable mixture of N-alkylated urea derivatives. The weak electron-withdrawing 4-bromobenzyl alcohol **2d** group diminished the yield of **4d** to a trace amount. It is important to emphasize that substituted benzyl alcohols produced complex mixtures of urea derivatives (e.g. **4b**) that were difficult to separate and characterize.



Scheme 10. Reaction of urea with various substituted benzyl alcohols

Table 6. Reaction of urea with various substituted benzyl alcohols.



R: **a** = H, **b** = CH_3, **c** = OCH_3, **d** = Br

Entry	Alcohol	**R**	Product, Yield **(%)**
1	**2a**	H	**4a** 82
2	**2b**	CH_3	**4b**, <10
3	**2c**	OCH_3	IM
4	**2d**	Br	**4d**, trace

IM: Intractable Mixture

2.6. Conclusion

In summary, we have developed an iridium catalyzed process for the N,N-dialkylation of urea with benzyl alcohol. Reaction parameters such as, base, temperature, and amount of reactant have a significant effect on the product yield. Optimized solvent-free conditions for N,N-dialkylation of urea employed $(Cp^*IrCl_2)_2$ (5 mol%), benzyl alcohol (3 equivalents), sodium acetate (5 mol %) at 120° for 17 hours. These conditions afforded N,N-dibenzylurea (**4a**) in 82% yield. None of the mono-alkylated product N-benzylurea (**3a**) or the symmetrical N,N'dibenzylurea (**5**) was obtained. Finally, substituted benzyl alcohols were not tolerated by the optimized conditions. The yields of the corresponding substituted benzyl urea derivatives were significantly diminished and complex mixtures of alkylated urea derivatives were obtained. Further studies will be necessary to identify reaction conditions suitable for the preparation of substituted benzyl urea derivatives from the corresponding substituted benzyl alcohols.

3. EXPERIMENTAL SECTION

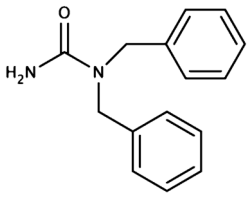
Chemicals not otherwise noted were purchased from Aldrich Chemical Company, Thermo Fisher Scientific Incorporation, and EMD Chemical Incorporation. The iridium catalyst $(Cp^*IrCl_2)_2$ was purchased from Alfa Aesar Company. Urea was dried in a desiccator for at least 24 hours before used. Silica gel thin layer chromatography (TLC) plates (E.M.D Chemical Inc., Kieselgel 60, F254, 0.02 – 0.025 mm layer, plastic and glass back) were visualized under UV light, iodine or phosphomolybdic acid. Flash silica gel 60 Å (230-400 mesh), and preparative thin layer chromatography (1000 micron) were used as purchased from Sorbent Technologies Company. ^{1}H and ^{13}C nuclear magnetic resonance spectra were recorded on a Varian 400 MHz spectrometer at room temperature in $CDCl_3$. NMR solvents were purchased from Cambridge Isotope Laboratories Inc. IR spectra were recorded on a Thermo Scientific Nicolet IR200 FT-IR spectrometer. Melting points was recorded on a SRS MPA160 apparatus and are uncorrected. Mass Spectral analyses were performed by Children Hospital Laboratories, New Orleans, Louisiana.

3.1. N-Alkylation of Urea with Benzyl Alcohol

General procedure: Urea (50 mg, 0.83 mmol, 1 equivalent), benzyl alcohol (1-3 equivalents), and $(Cp^*IrCl_2)_2$ (16.6 mg, 5 mol %) were added to a sealed pressure tube. Base (5 mol %) and 3-5 ml of solvent were used according to described reaction conditions. The reaction mixture was heated and stirred for 17h on silicon oil bath. Reaction temperatures were varied 80-160 °C as specified. The reaction mixture was allowed to cool to room temperature and water (10 mL) was added. The mixture was

extracted with ethyl acetate (3×10 mL) and the combined organic layers were dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure, and the residue was purified using flash silica gel chromatography with (hexane:ethyl acetate) or preparative thin layer chromatography to furnish the product.

N,N-Dibenzylurea (4a)



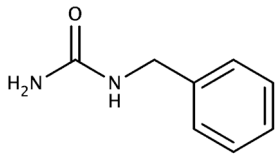
Solvent-free, base-free conditions: Urea (50 mg, 0.83 mmol, 1 equivalent), benzyl alcohol (270 mg, 2.4 mmol, 3 equivalent), and $(Cp^*IrCl_2)_2$ (17 mg, 5 mol %) were added to a sealed pressure tube. The reaction mixture was heated at 120, 140, and 160 °C and stirred for 17h on silicon oil bath. The reaction mixture was allowed to cool to room temperature and water (10 mL) was added. The mixture was extracted with ethyl acetate (3×10 mL) and the combined organic layers were dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure. The residue was visualized by TLC and showed only starting materials.

Solvent and base conditions: Urea (50 mg, 0.83 mmol, 1 equivalent), benzyl alcohol (270 mg, 2.4 mmol, 3 equivalent), and $(Cp^*IrCl_2)_2$ (17 mg, 5 mol %), toluene (5 ml) and potassium *tert*-butoxide (5.0 mg, 5 mol %) were added to a sealed pressure tube. The reaction mixture was heated at 160 °C and stirred for 17h on silicon oil bath. The reaction mixture was allowed to cool to room temperature and water (10 mL) was added. The

mixture was extracted with ethyl acetate (3×10 mL) and the combined organic layers were dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the residue was purified using flash silica gel chromatography with (hexane:ethyl acetate 60:40) to furnish 4a as a white solid (18 mg, 9%).

Solvent-free optimized conditions: Urea (50 mg, 0.83 mmol, 1 equivalent), benzyl alcohol (270 mg, 2.4 mmol, 3 equivalent), and $(Cp^*IrCl_2)_2$ (17 mg, 5 mol %) and sodium acetate (6.0 mg, 5 mol %) were added to a sealed pressure tube. The reaction mixture was heated at 120 °C and stirred for 17h on silicon oil bath. The reaction mixture was allowed to cool to room temperature and water (10 mL) was added. The mixture was extracted with ethyl acetate (3×10 mL) and the combined organic layers were dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the residue was purified using flash silica gel chromatography with (hexane:ethyl acetate 60:40) to furnish **4a** as a white solid (63 mg, 82%); mp 121-123 °C (Lit mp [22]: 121-125 °C). IR (KBr), 3400, 3326, 1590, 1482, 1439, 1280, 690; ^{1}H NMR (400 MHz, $CDCl_3$) δ : 7.31-7.16 (m, 10H, aromatic), 6.08 (s, 2H, NH_2), 4.33 (s, 4H, CH_2); ^{13}C NMR (400 MHz, $CDCl_3$) δ 158.6, 137.4, 129.1, 127.8, 127.4, 50.7; MS, *m*/*z*: [$(M+H)^+$] calcd. for $C_{15}H_{17}N_2O$: 241.31. Found, 241.09.

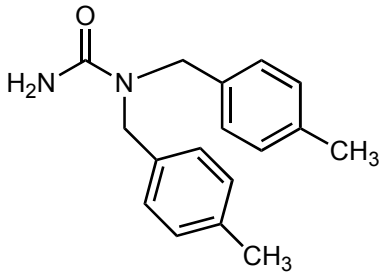
N-Benzylurea (3a)



Urea (50 mg, 0.83 mmol, 1 equivalent), benzyl alcohol (270 mg, 2.4 mmol, 3 equivalent), and $(Cp^*IrCl_2)_2$ (17 mg, 5 mol %) and sodium acetate (6.0 mg, 5 mol %) were added to a sealed pressure tube. The reaction mixture was heated at 120 °C and stirred for 17h on silicon oil bath. The reaction mixture was allowed to cool to room temperature and water (10 mL) was added. The mixture was extracted with ethyl acetate (3×10 mL) and the combined organic layers were dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the residue was purified using flash silica gel chromatography with (hexane : ethyl acetate 60:40) to furnish **3a** as a white solid (7.5 mg, 6%); mp 91-93 °C (Lit mp [23]: 72-74 C). IR (KBr) 3410, 1683, 1612, 1404, 1333, 717; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.21 (m, 5H, aromatic), 4.30 (s, 2H, CH_2); ^{13}C NMR (400 MHz, $CDCl_3$) δ 158.4, 139.3, 128.9, 127.6, 127.6, 44.8.

3.2. N-Alkylation of Urea with Substituted Benzyl Alcohol

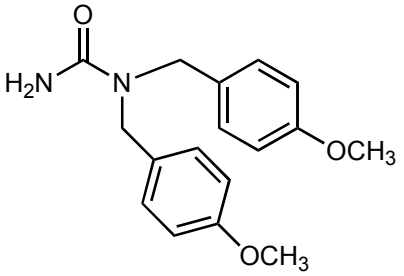
N,N-Di(4-methyl)benzyl urea (4b)



Urea (100 mg, 1.67 mmol, 1 equivalent), 4-methylbenzyl alcohol (610 mg, 5.0 mmol, 3 equivalent), and $(Cp^*IrCl_2)_2$ (33 mg, 5 mol %) and sodium acetate (11.0 mg, 5 mol %) were added to a sealed pressure tube. The reaction mixture was heated at 120 °C and stirred for 17h on silicon oil bath. The reaction mixture was allowed to cool to room

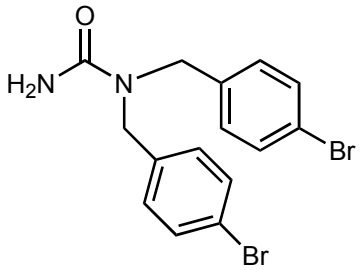
temperature and water (10 mL) was added. The mixture was extracted with ethyl acetate (3×10 mL) and the combined organic layers were dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the residue was purified using preparative TLC with (hexane:ethyl acetate 60:40) to furnish **4b** as a white solid (20 mg, 4%); mp 168-169 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.16-7.11 (d, J = 7.8 Hz, 8H, aromatic), 4.87 (s, 4H, s, CH_2), 2.25 (s, 6H, CH_3); ^{13}C NMR (400 MHz, $CDCl_3$), δ 163.2, 139.5, 133.4, 129.1, 128.8, 53.7.

N,N-Di(4-methoxy)benzyl urea (4c)



Urea (100 mg, 1.67 mmol, 1 equivalent), 4-methoxybenzyl alcohol (690 mg, 5.0 mmol, 3 equivalents), and $(Cp^*IrCl_2)_2$ (33 mg, 5 mol %) and sodium acetate (11.0 mg, 5 mol %) were added to a sealed pressure tube. The reaction mixture was heated at 120 °C and stirred for 17h on silicon oil bath. The reaction mixture was allowed to cool to room temperature and water (10 mL) was added. The mixture was extracted with ethyl acetate (3×10 mL) and the combined organic layers were dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure and intractable mixture of N-alkylated urea derivatives was observed and could not be separated under flash silica gel or preparative TLC.

N ,N-Di(4-bromo)benzyl urea (4d)



Urea (100 mg, 1.67 mmol, 1 equivalent), 4-bromobenzyl alcohol (934 mg, 5.0 mmol, 3 equivalent), and $(Cp^*IrCl_2)_2$ (33 mg, 5 mol %) and sodium acetate (11.0 mg, 5 mol %) were added to a sealed pressure tube. The reaction mixture was heated at 120 °C and stirred for 17h on silicon oil bath. The reaction mixture was allowed to cool to room temperature and water (10 mL) was added. The mixture was extracted with ethyl acetate (3×10 mL) and the combined organic layers were dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the residue was purified using preparative TLC with (hexane:ethyl acetate 60:40) to furnish **4d** as a white solid (5 mg, 1%); mp 139-142 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.55-7.12 (d, J = 7.8 Hz, 8H, aromatic), 4.87 (s, 4H, s, CH_2); ^{13}C NMR (400 MHz, $CDCl_3$) δ: 163.2, 135.4, 131.1, 130.1, 53.8.

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