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A Novel Synthesis of Disubstituted Ureas Using Titanium(IV) Isopropoxide and Sodium Borohydride

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Abstract: *This paper describes a high yield preparation of unsymmetrically disubstituted ureas by a titanium(IV) isopropoxide /sodium borohydride mediated reductive amidation of aromatic aldehydes with monosubstituted ureas.*

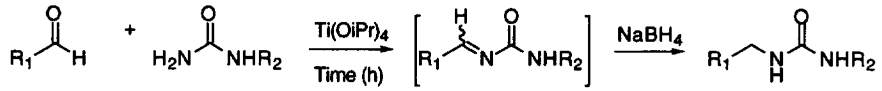
There are a variety of methods available for the preparation of substituted ureas. In the presence of selenium[1] or sulfur,[2] symmetrically substituted ureas can be prepared by treating a primary amine or ammonia with carbon monoxide. Substituted ureas can also be formed when isocyanates are added to ammonia, primary amines, and secondary amines.[3] Primary amines have been found to add to carbon dioxide in the presence of diphenyl phosphite and pyridine yielding symmetrically substituted ureas.[4] The reductive amination[5] of aldehydes and ketones with primary and secondary amines in the presence of titanium(IV) isopropoxide and sodium borohydride was recently described by Bhattacharya.[6] Bhattacharya reported that titanium(IV) isopropoxide acts as a Lewis acid catalyst and as an excellent water scavenger, producing imines which are subsequently reduced by sodium borohydride.[6] Another plausible mechanism proposes that the imine can be reduced either directly or indirectly via a stable titanium tetrahedral intermediate.[5,7,8]

We now report that titanium(IV) isopropoxide is an effective Lewis acid catalyst for the formation of imines from ureas and aromatic aldehydes and upon subsequent reduction with $NaBH_4$ produces unsymmetrically disubstituted ureas in high yield. This method provides advantages over the aforementioned methods in that it does not involve a gas phase substrates (ie. CO and CO_2) or highly toxic isocyanates and it is able to produce a variety of unsymmetrically substituted ureas. Furthermore, it has been demonstrated that titanium(IV) isopropoxide is compatible with a variety of functional groups such as lactams, acetonides, acetals, and tert-butyldimethylsiyl ethers.[7,8] This method is, however, limited by the reactivity of the aldehyde. Unfortunately, aldehydes with an α–hydrogen do not undergo selective reductive amidation with ureas under the described conditions. In order to determine the scope of this reaction a number of different aldehydes were allowed to react with methyl urea and benzyl urea respectively.

The reaction is typically carried out by charging the aldehyde (1 eq.), urea (1.5 eq.) and titanium(IV) isopropoxide (1.7 eq.) to THF and stirring at the designated temperature and time (Table 1). Once formation of the imine or tetrahedral intermediate is complete, as evidenced by ^{1}H NMR, it is reduced with sodium borohydride (0.5 eq.). For entry **2a**, the tetrahedral intermediate is formed exclusively when the reaction is carried out in isopropanol rather than THF and is reduced to the desired product in 75% yield.

Inspection of Table 1 reveals a definite trend in reactivity which can be explained in terms of the electrophilicity of the aldehyde and the nucleophilic character of the ureas. Highly electrophilic aldehydes (entries **2a**, **2b**, **3a**, **3b**, **4a**, and **4b**) were readily reductively amidated at ambient temperature due to the presence of an electron withdrawing group on the aromatic aldehyde. Entries **1a** and **1b** required much longer reaction time to form the corresponding imines due to lack of an activating group. Entries **5a** and **5b** were even further deactivated as the aromatic aldehyde possessed an electron donating methoxy group. The results for entry **6** demonstrated that the phenol group was incompatible in this reaction. Entries **7**, **8**, and **10** did not form the corresponding disubstituted ureas, most likely due to the presence of an α-hydrogen. It is proposed that substrates possessing an α-hydrogen can undergo tautomerization and form the corresponding enamines which decomposed under the reactions conditions. Also, in a control study, in the presence of titanium(IV) isopropoxide these aldehydes undergo complete decomposition after 26h at 55 °C as observed via ^{1}H NMR. Entry **9** proceeded very slowly and in poor yield because of competing side reactions. This method of synthesizing disubstituted ureas from aromatic aldehydes and monosubstituted ureas with titanium(IV) isopropoxide and sodium borohydride proceeds readily and in excellent yield.

Table 1. Representative Reductive Amidations of Aldehydes and Monosubstituted Ureas with Titanium(IV) Isopropoxide and Sodium Borohydride



Entry	Aldehyde	Urea	Time (h)	Product	Yield (%)*
1a	$R_1=C_6H_5$	$R_2=CH_3$	24, 22°C	1c, $R_1=C_6H_5$, $R_2=CH_3$	53
1b	$R_1=C_6H_5$	$R_2=Bn$	24, 22°C	1d, $R_1=C_6H_5$, $R_2=Bn$	86
2a	$R_1=2\text{-}BrC_6H_5$	$R_2=CH_3$	4.5, 22°C	2c, $R_1=2\text{-}BrC_6H_5$, $R_2=CH_3$	85
2b	$R_1=2\text{-}BrC_6H_5$	$R_2=Bn$	4.5, 22°C	2d, $R_1=2\text{-}BrC_6H_5$, $R_2=Bn$	92
3a	$R_1=2\text{-}NO_2C_6H_5$	$R_2=CH_3$	4.5, 22°C	3c, $R_1=2\text{-}NO_2C_6H_5$, $R_2=CH_3$	78
3b	$R_1=2\text{-}NO_2C_6H_5$	$R_2=Bn$	4.5, 22°C	3d, $R_1=2\text{-}NO_2C_6H_5$, $R_2=Bn$	89
4a	$R_1=3\text{-}NO_2C_6H_5$	$R_2=CH_3$	4.5, 22°C	4c, $R_1=3\text{-}NO_2C_6H_5$, $R_2=CH_3$	79
4b	$R_1=3\text{-}NO_2C_6H_5$	$R_2=Bn$	4.5, 22°C	4d, $R_1=3\text{-}NO_2C_6H_5$, $R_2=Bn$	94
5a	$R_1=4\text{-}CH_3OC_6H_5$	$R_2=CH_3$	24, 55°C	5c, $R_1=4\text{-}CH_3OC_6H_5$, $R_2=CH_3$	39
5b	$R_1=4\text{-}CH_3OC_6H_5$	$R_2=Bn$	26, 55°C	5d, $R_1=4\text{-}CH_3OC_6H_5$, $R_2=Bn$	63
6	$R_1=4\text{-}HOC_6H_5$	$R_2=CH_3$	19, 55°C	no product	0
7	$R_1=CH_3(CH_2)_4\text{-}$	$R_2=CH_3$	24, 55°C	no product	0
8	$R_1=\underbrace{CH_2(CH_2)_4CH}\text{-}$	$R_2=CH_3$	24, 55°C	no product	0
9	$R_1=trans\text{-}C_6H_5CHCH\text{-}$	$R_2=Bn$	48, 55°C	9b, $R_1=trans\text{-}C_6H_5CHCH$, $R_2=Bn$	15
10	$R_1=C_6H_5CH_2CH_2\text{-}$	$R_2=Bn$	48, 55°C	no product	0

*Isolated yield corrected for weight percent purity.

General Procedure for the reductive amidation of activated aldehydes and monosubstituted ureas. A mixture of 2-bromobenzaldehyde (0.63mL, 5.4 mmol, 1.0 equiv.), methyl urea (0.60g, 8.1mmol, 1.5 equiv.), and titanium(IV) isopropoxide (2.71mL, 9.2 mmol, 1.7 equiv.) were slurried in 10 mL of THF. This slurry was stirred at room temperature under nitrogen. After 4.5 hours, the ^1H NMR spectrum showed that the aldehyde peak was no longer present. The reaction mixture was then cooled to 0 °C and sodium borohydride (0.102g, 2.7mmol, 0.5 equiv.) was added. The ice bath was removed and the resulting slurry was allowed to stir for 2 hours. The slurry was again cooled to 0 °C and quenched by dropwise addition of 20mL of 1.0N HCl and 20 mL of water, giving a 4:1 ratio of water to THF. The product precipitated out during the acidic workup and was filtered, washed with water, and dried in a vacuum oven (40 °C, 10h). The product **2c** was recrystallized from acetonitrile.

Entries **1a**, **1b**, **2a**, **2b**, **3a**, **3b**, **4a**, and **4b** were all carried out in the same manner with possible exception to the time required to form the imine as noted in Table 1. In entries **5a**, **5b**, **6**, **7**, and **8**, 3.0 equiv. of the respective urea and 3.5 equiv. of titanium(IV) isopropoxide were used. Entries **9** and **10** required 3.0 equiv. of benzyl urea and 5.0 equiv. of titanium(IV) isopropoxide. Products **1c** and **5c** the did not precipitate out of solution. In these cases, the solution was saturated with sodium chloride and the product was isolated via multiple extractions with THF. The THF extracts were combined and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel (5% methanol / 95% methylene chloride). Compounds **3c** and **4c** were recrystallized from ethyl acetate / acetonitrile (6:1), **1d** was recrystallized from 100% acetonitrile, **2d** was recrystallized from 100% ethanol, **3d** and **4d** were recrystallized from ethanol / water (6:1), **5d** was recrystallized from acetonitrile/water (6:1), and **9b** was purified by flash chromatography on silica gel (4% methanol / 96% methylene chloride).

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