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An efficient synthesis of β-acylureas via a three-component, one-pot synthesis using TCS/$ZnCl_2$

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ABSTRACT

A simple and efficient one-pot, three-component synthesis of new trisubstituted ureas containing diastereotopic protons is achieved via the reaction of aromatic aldehydes, aromatic ketones, and dimethyl cyanamide using a TCS/$ZnCl_2$ reagent mixture at room temperature.

In multicomponent reactions (MCRs), three or more substrates react in a single reaction vessel to form new products that contain structural units of all the components. These types of reactions are important in organic and medicinal chemistry because they allow highly sophisticated polyfunctional molecules to be obtained through simple one-pot procedures. Multicomponent reactions have been successfully employed to generate highly diverse combinatorial libraries for high-throughput screening of biological and pharmacological activities.[1–5] The use of three or more building blocks in a one-pot, high-yielding multicomponent reaction leads to a wide structural and functional diversity combined with excellent combinatorial efficiency. Industrial and academic research has made use of MCR strategies as efficient and cost-effective tools for combinatorial synthesis.[6–8] The development of novel MCRs is a challenging task since one has to consider not only the reactivity match of the starting materials but also the reactivity of the intermediate molecules generated in situ, their compatibility, and their compartmentalization.[9]

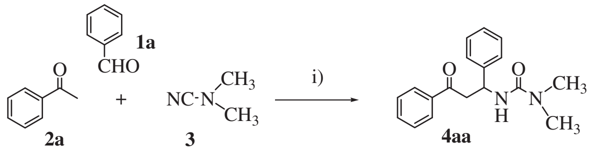
Urea derivatives have been reported as an important class of compounds in organic, bioorganic, supramolecular, and medicinal chemistry.[10] A few reports are available on the synthesis of β-acylureas by reacting amines with phosgene or substituted isocyanates[10,11] which are considered as highly toxic and unstable materials. In the present work, we describe a new practical approach for the synthesis of some novel trisubstituted urea derivatives.

Many reagents have been derived from tetrachlorosilane (TCS).[12] In continuation of our investigations on the synthesis of novel alicyclic and heterocyclic compounds, and the design of novel multicomponent reactions using a binary catalyst derived from TCS as an in situ reagent,[13] we have developed an efficient protocol for the synthesis of 1,1-dimethyl-3-(3-oxo-1,3-diphenylpropyl)urea (**4aa**) in good yield. The reaction occurs via a three-component, one-pot reaction between benzaldehyde (**1a**), acetophenone (**2a**), and dimethyl cyanamide (**3**) using TCS/$ZnCl_2$ in methylene chloride as the solvent at room temperature (Scheme 1).

As a part of an ongoing study to investigate the optimum conditions for these reactions, we studied the efficacy of the promoter type, molar ratio, and solvent. The results obtained are summarized in Table 1.

It was found that the best results were obtained by using a 1:1:1:3 ratio of aldehyde, acetophenone, dimethyl cyanamide, and TCS/$ZnCl_2$, respectively, in CH_2Cl_2 (Table 1, entry 3). These results prompted us to explore the potential of this protocol for the synthesis of various trisubstituted ureas. The results are summarized in Scheme 2 and Table 2.

From the results obtained it was apparent that the reaction time was shorter and the yield was higher for the one-pot condensations of aldehydes or acetophenones containing an electron-donating group (CH_3), relative to the unsubstituted reactants. However,



Reagents and conditions: i) TCS/$ZnCl_2$, CH_2Cl_2, r.t.

Scheme 1. Synthesis of 1,1-dimethyl-3-(3-oxo-1,3-diphenylpropyl)urea **4aa**.

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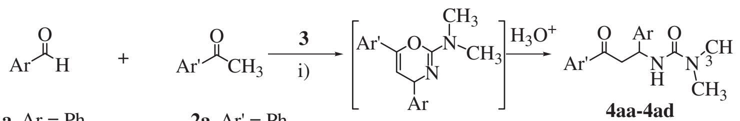
the presence of electron-withdrawing substituents (Cl, Br) led to longer reaction times and lower yields (Tables 2).

The structures of the obtained β-acylureas were elucidated by spectroscopic methods. The IR spectra showed peaks at ν = 3396–3295, 1689–1660, and 1633–1623 cm^{-1} corresponding to NH, $COCH_2$, and the urea carbonyl $(CH_3)_2NCONH$ groups, respectively. The ^1H NMR spectra of the synthesized products revealed singlets for $–N(CH_3)_2$, two double doublets and mutiplet signals for the diastereotopic protons (CH_2CH), and broad NH signals. The ^{13}C NMR spectrum of compound (**4ab**) showed two characteristic signals at δ = 199.21 for the ketone (CO) and at 144.28 for the urea $[(CH_3)_2NCONH]$ carbonyl groups, at 142.31–125.83 for $C_{Ar}H$,

Table 1
Effect of promoters and solvents on the yield and reaction time for the one-pot synthesis of 1,1-dimethyl-3-(3-oxo-1,3-diphenylpropyl)urea (**4aa**)

Entry	Promoter (mmol)	Solvent	Time (h)	Yield (%)
1	TCS/$ZnCl_2$ (10)	CH_2Cl_2	20	50
2	TCS/$ZnCl_2$ (20)	CH_2Cl_2	10	65
3	TCS/$ZnCl_2$ (30)	CH_2Cl_2	6	85
4	TCS/$ZnCl_2$ (30)	THF	20	35
5	TCS/$ZnCl_2$ (30)	1,4-dioxane	20	40
6	TCS (30)	CH_2Cl_2	30	20
7	$ZnCl_2$ (30)	CH_2Cl_2	30	15
8	TCS/$SnCl_2$ (30)	CH_2Cl_2	30	45
9	TCS/$FeCl_3$ (30)	CH_2Cl_2	30	32



1a, Ar = Ph-
1b, Ar = 4-F-C_6H_4-
1c, Ar = 4-Cl-C_6H_4-
1d, Ar = 3-Br-C_6H_4-
1e, Ar = 2-thienyl
1f, Ar = naphthyl

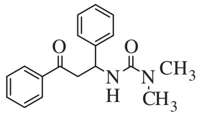
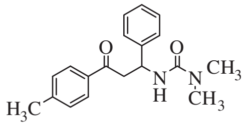
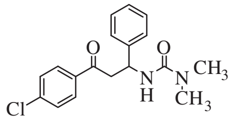
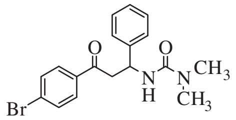
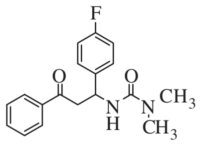
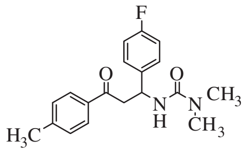
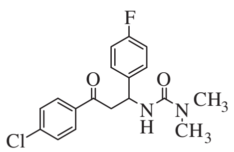
2a, Ar' = Ph-
2b, Ar' = 4-CH_3-C_6H_4-
2c, Ar' = 4-Cl-C_6H_4-
2d, Ar' = 4-Br-C_6H_4-

4aa-4ad
4ba-4bd
4ca
4da-4dd
4ea
4fa

Reagents and conditions: i) TCS/$ZnCl_2$, CH_2Cl_2, r.t.

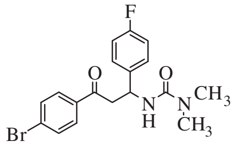
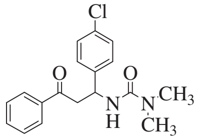
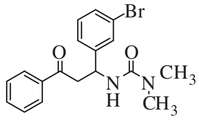
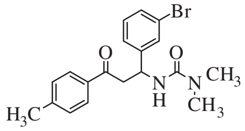
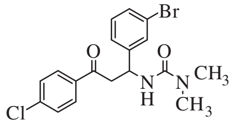
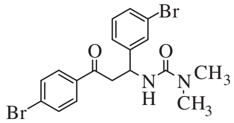
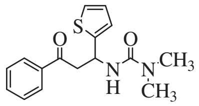
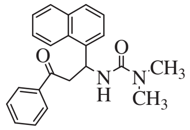
Scheme 2. Synthesis of trisubstituted ureas.

Table 2
Reaction of dimethyl cyanamide (**3**) with various aldehydes **1** and ketones **2**

Entry	Aldehyde	Ketone	Product	Time (h)	Yield (%)
1	**1a**	**2a**		6	85
2	**1a**	**2b**		5	89
3	**1a**	**2c**		8	80
4	**1a**	**2d**		10	78
5	**1b**	**2a**		8	87
6	**1b**	**2b**		7	88
7	**1b**	**2c**		9	85

(*continued on next page*)

Table 2 (*continued*)

Entry	Aldehyde	Ketone	Product	Time (h)	Yield (%)
8	**1b**	**2d**		10	82
9	**1c**	**2a**		9	77
10	**1d**	**2a**		11	78
11	**1d**	**2b**		10	83
12	**1d**	**2c**		12	75
13	**1d**	**2d**		12	72
14	**1e**	**2a**		8	80
15	**1f**	**2a**		12	70

51.58 for CH_2, 43.62 for CHNH, 36.15 for $2CH_3$ and 21.60 CH_3 ppm (see also the Supplementary data).

In conclusion, the synthesis of β-acylureas containing diastereotopic protons in good to excellent yields via the MCR of dimethyl cyanamide, an aromatic ketone, and an aromatic aldehyde using a binary reagent (TCS/$ZnCl_2$) and methylene chloride as solvent has been described.[14] The reaction products were characterized by IR, MS, ^1H NMR, ^{13}C NMR, and elemental analysis.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.01.066.

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14. In a dry two-necked round bottomed flask equipped with a rubber septum, a magnetic stirring bar, and a condenser, a mixture of ketone (5 mmol), aldehyde (5 mmol), dimethyl cyanamide (5 mmol), anhydrous $ZnCl_2$ (15 mmol), in CH_2Cl_2 (20 ml) was allowed to stir with exclusion of moisture at room temperature for 5 min. Tetrachlorosilane (15 mmol) was then added and the mixture was stirred for the specified time (Table 2). The mixture was poured onto ice-cold H_2O (~100 ml), neutralized with aq Na_2CO_3, extracted with $CHCl_3$ (3×30 ml) and the extract was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the obtained residue was purified by preparative thin layer chromatography to give products **4**. 1,1-Dimethyl-3-(3-oxo-1,3-diphenylpropyl)urea (**4aa**) R_f 0.33 (pet. ether/EtOAc, 2:1), mp 164–6 °C. IR (KBr) ν: 3332, 3062, 2926, 1686, 1626, 1533. ^{1}H NMR δ_H (500 MHz, $CDCl_3$): 2.92 (s, 6H, $2CH_3$), 3.41–3.46 (dd, 1H, J = 16.4, 6.1 Hz, CH_2CH), 3.71–3.75 (dd, 1H, J = 16.4, 5.3 Hz, CH_2CH), 5.41–5.42 (m, 1H, CH_2CH), 5.81 (b, 1H, NH), 7.22–8.08 (m, 10H, ArH). MS (EI 70 eV) *m*/*z*: 296 (M^+), 224, 191, 72. Anal. Calcd for $C_{18}H_{20}N_2O_2$ (296.15): C, 72.95; H, 6.80; N, 9.45. Found: C, 72.87; H, 6.77; N, 9.41. 1,1-Dimethyl-3-(3-oxo-1-phenyl-3-*p*-tolylpropyl)urea (**4ab**) R_f 0.32 (pet. ether/EtOAc, 2:1), mp 118 °C. IR (KBr) ν: 3297, 3046, 2929, 1662, 1624, 1523. ^{1}H NMR δ (300 MHz, $CDCl_3$): 2.40 (s, 3H, CH_3), 2.95 (s, 6H, $2CH_3$), 3.38–3.45 (dd, 1H, J = 16.5, 5.7 Hz, CH_2CH), 3.66–3.73 (dd, 1H, J = 16.4, 5.4 Hz, CH_2CH), 5.40–5.41 (m, 1H, CH_2CH), 5.91 (br s, 1H, NH), 7.17–7.82 (m, 9H, ArH). ^{13}C NMR δ (75 MHz, $CDCl_3$): 199.21 (C=O), 144.28 ($(CH_3)_2$NCONH), 142.31–125.83 (10 ArC), 51.58 (CH_2), 43.62 (CHNH), 36.15 ($2CH_3$), 21.60 (CH_3). MS (EI 70 eV) *m*/*z*: 310 (M^+), 222, 119, 72. Anal. Calcd for $C_{19}H_{22}N_2O_2$ (310.39): C, 73.52; H, 7.14; N, 9.03. Found: C, 73.45; H, 7.12; N, 9.00. 3-[3-(4-Chlorophenyl)-1-(4-fluorophenyl)-3-oxopropyl]-1,1-dimethylurea (**4bc**) R_f 0.26 (pet. ether/EtOAc, 2:1), mp 147 °C. IR (KBr) ν: 3320, 3064, 2927, 1688, 1624, 1535. ^{1}H NMR δ (200 MHz, $CDCl_3$): δ (ppm) 2.69 (s, 6H, $2CH_3$), 3.15–3.18 (dd, 1H, J = 16, 6.2 Hz, CH_2CH), 3.41–3.43 (dd, 1H, J = 16, 5.2 Hz, CH_2CH), 5.12–5.15 (m, 1H, CH_2CH), 5.43 (br s, 1H, NH), 6.70–7.71 (m, 8H, ArH). MS (EI 70 eV) *m*/*z*: 348 (M^+), 276, 139, 72. Anal. Calcd for $C_{18}H_{18}ClFN_2O_2$ (348.8): C, 61.98; H, 5.20; N, 8.03. Found: C, 61.93; H, 5.16; N, 8.00.