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Hypervalent Iodine(III)-Mediated Regioselective N-Acylation of 1,3-Disubstituted Thioureas

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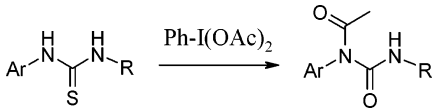

Reaction of asymmetrical 1,3-disubstituted thioureas with diacetoxyiodobenzene (DIB) produces regioselectively *N*-acetylurea in shorter time. Regioselectivity is dependent on the pK_a's of the amine attached to the thiourea moiety with acylation taking place toward the amine having a lower pK_a. This is the first example of DIB being employed as an N-acetylating agent. A mechanism for this novel transformation is also proposed. Mild reaction conditions, shorter reaction times, high efficiencies, environmentally benign methods, and facile isolation of the desired product make the present methodology a most suitable alternative.

Interest in the polyvalent iodine compounds has experienced an explosive development in the last two decades, mainly due to the useful oxidizing properties combined with their benign environmental character and easy commercial avaibility. As an oxidants, hypervalent iodine(III) or λ^3-iodanes reagents are widely recognized as alternatives to highly toxic heavy metal oxidants such as lead-, mercury-, and thallium-based reagents.[1] In addition to acting as an useful oxidizing agents, derivatives of hypervalent iodine reagent occupy an important place in the realm of natural and synthetic organic chemistry because it has found potential applications for the construction of carbon−heteroatom and carbon−carbon bonds.[1,2]

Ureas and thioureas are useful synthons for the construction of heterocyclic compounds.[3] *N*-Acylureas have found important applications in agrochemicals and pharmaceuticals.[4] Dopamine D2 agonist cabergoline having an *N*-acyl derivative is an anti-Parkinson agent.[5] These compounds act as interesting semi-crystalline materials[6] and auxiliaries for the synthesis of chiral cyclic carboxylic acids.[7] Derivatives of acylurea have been used for the allylation of sulfoxides,[8a] Claisen rearrangement,[8b] Diels−Alder reaction,[8c,d] nucleophilic addition of TMSCN,[8e] Michael addition,[8f] and enantioselective Strecker and Mannich reactions.[8g−i]

The reported methods for the synthesis of *N*-acylurea are by the reaction of substituted ureas with acyl chlorides or acids at elevated temperature and reaction of amides with isocyanates or carbodiimides.[9a] The reported method produces a non-regioselective product for unsymmetrical urea, and a regioselective product is produced from symmetrical urea or by a carbodiimide approach.[10] A similar N-acylation of thioureas using $Mn(OAc)_3$ was disclosed recently by Mu et al.[11] In this paper, we have demonstrated an unprecedented regioseletive N-acetylation of disubstituted thioureas leading to *N*-acetyl ureas using diacetoxyiodobenzene (DIB) as shown in Scheme 1.

In organic chemistry, $Mn(OAc)_3$ has been most commonly used in the generation of carbon-centered radicals from various carbonyl compounds and their oxidative addition to alkenes.[12]

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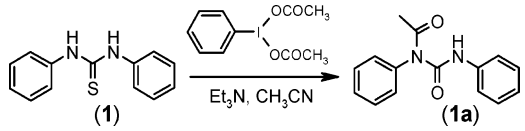
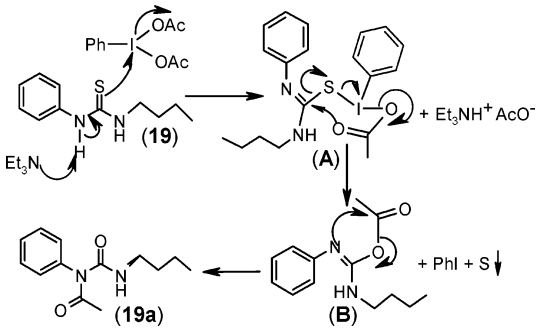
SCHEME 1. N-Acylation of Urea from Thiourea



SCHEME 2. Proposed Mechanism of Formation of *N*-Acylurea



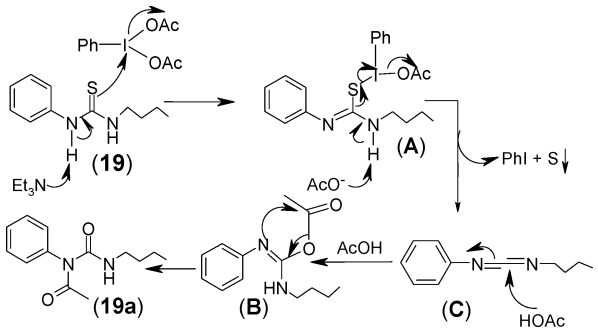
However, significant drawbacks to the use of $Mn(OAc)_3$ are the harsh reaction conditions and its poor solubility in organic solvents. On the other hand, diacetoxyiodobenzene in the presence of iodine or under photochemical conditions generates radicals. This similarity between diacetoxyiodobenzene (DIB) with $Mn(OAc)_3$ and the N-acetylating ability[11] of the latter reagent prompted us to use the metal-free reagent diacetoxyiodobenzene for the preparation of *N*-acetylurea.

In a typical reaction, an equimolar mixture of 1,3-diphenylthiourea **1**, triethylamine, and diacetoxyiodobenzene (DIB) was mixed together in acetonitrile, and the reaction mixture was stirred at room temperature. The reaction was completed within 5 min giving N-acetylated product **1a** in good yield. The proposed mechanism for the formation of N-acetylated product is shown in Scheme 2.

The sulfur atom of the 1,3-disubstituted-thiourea attacks on the thiophilic iodine of $PhI(OAc)_2$ displaying one of the acetate groups, giving intermediate **A**, which is then followed by an intramolecular nucleophilic attack of the carbonyl group of the acetate on the imine carbon giving sulfur and phenyliodide as byproducts. Formation of elemental sulfur and phenyl iodide has actually been confirmed by isolating them. The resultant 2-acetyl-1,3-disubstituted isourea (**B**) rearranges to 1-acetyl-1,3-disubstituted-urea **19a** as shown in Scheme 2. The structure of N-acylated product **1a** has been confirmed by crystal X-ray crystallography.[13]

However, when the reaction of **1** was carried out in the presence of 1 equiv of propionic acid and an additional 1 equiv of triethylamine it gave N-acetylated product **1a** along with the formation of propionylated product **1a′** in a ratio of 58:42. In a second experiment, the reaction was carried out with a 5-fold excess of propionic acid and triethylamine, the products **1a** and **1a′** obtained were in the ratio 17:83. The formation of propionylated product **1a′** rules out any possibility of an intramolecular mechanism as proposed in Scheme 2.

SCHEME 3. Proposed Mechanism of Formation of *N*-Acylurea



Alternatively, a mechanism involving the intermediacy of carbodiimide seems to be a reasonable proposition as shown in Scheme 3. Reductive β-elimination of λ^3-iodane intermediate (**A**) with the expulsion of sulfur will produce carbodiimide (**C**) (Scheme 3), which on reaction with acetic acid liberated in the medium would give 2-acetyl-1,3-disubstituted-isourea. Infrared spectral analysis of the reaction mixture showed a characteristic peak for carbodiimide group at 2138 cm^{-1}. Further, the isolation of stable carbodiimide **10a** (Table 1) is testimony to this fact and supports the mechanism proposed in Scheme 3. However, similar reactions were not successful for ureas, probably due to the lower acidity of the NH protons in urea and lesser affinity of oxygen toward iodine compared to sulfur present in thioureas.

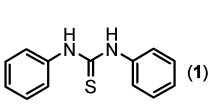
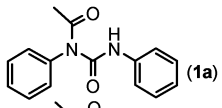
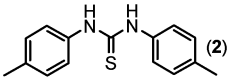
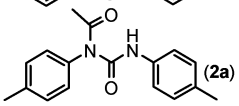
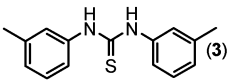
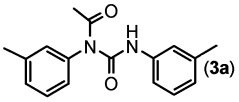
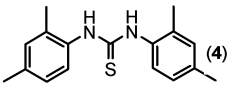
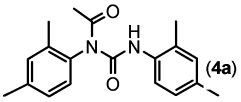
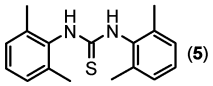
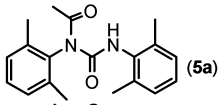
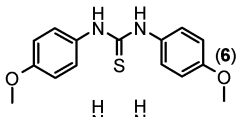
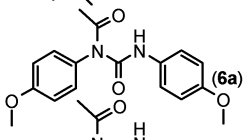
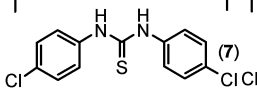
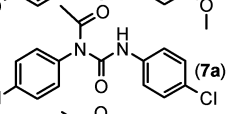
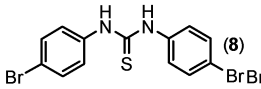
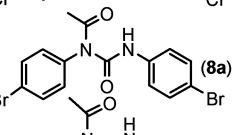
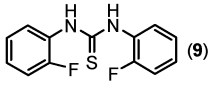
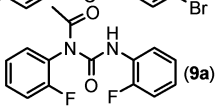
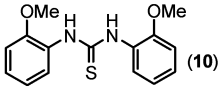
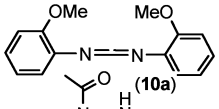
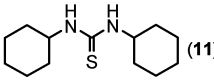
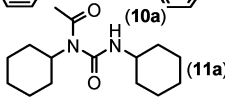
Several symmetrical thioureas **2**−**9** having various substituents in the phenyl ring gave their corresponding mono N-acylated ureas **2a**−**9a** within 5 min giving excellent yields of the products as shown in Table 1, but for uniformity all of the reactions were allowed to stir for 15 min. When the reaction was performed with 1,3-bis(2-methoxyphenyl)thiourea **10**, no N-acetylated product was observed, and the only isolated product obtained was found to have a bis(2-methoxyphenyl)carbodiimide **10a** moiety. The stability of carbodiimide **10a** can be explained by the neighboring group participation of the *o*-methoxy group from the adjacent phenyl ring as shown in Scheme 4. Aliphatic thiourea **11** does not undergo N-acylation; this may be due to difficulty in deprotonating due to the substantial basic character of cyclohexylamine (pK_a 10.66). This observation is consistent with the N-acylation using $Mn(OAc)_3$.[11]

Having successfully synthesized a series of N-acylated ureas, we were interested in regioselective N-acylation of unsymmetrical thiourea. We have found that the larger the difference between the pK_a's of the precursors amines in thiourea the greater the regioselectivity of N-acylation with preferential acylation taking place toward the amine having lower pK_a. Unsymmetrical thiourea **12** would form an unsymmetrical carbodiimide as the intermediate. The attack of acetic acid on unsymmetrical carbodiimide would lead to the protonation toward the amine having higher pK_a unaffecting the imine group on the other side. The resultant isourea on rearrangement would yield N-acylated product in regioselective manner. For 1-phenyl-3-*p*-tolylthiourea (**12**), the phenyl side is acylated 60% compared to *p*-tolyl side (40%) as evident from the ^1H NMR. The measured pK_a's of aniline and *p*-methylaniline are 4.61 and 5.08, respectively, supporting our arguments and the mechanism involving carbodimide intermediate (Scheme 3). The measured pK_a's of both *p*-chloro- (4.15) and *p*-bromoanilines (3.86) are

(13) Crystallographic data for compound **1a** have been deposited at the Cambridge Crysallographic Data Centre (deposition no. CCDC-669356). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. [fax (int)] (01223 336033; email: deposit@ccdc.cam.ac.uk].

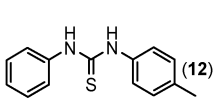
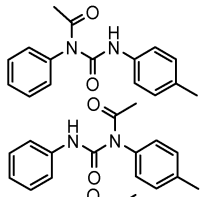
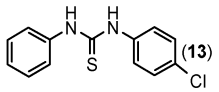
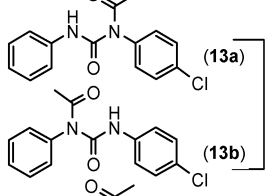
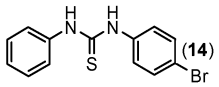
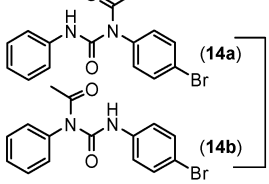
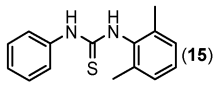
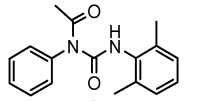
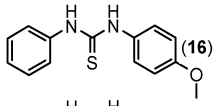
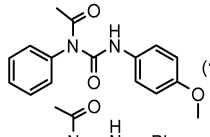
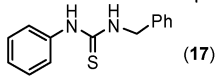
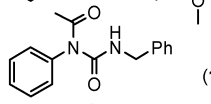
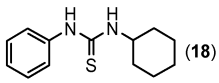
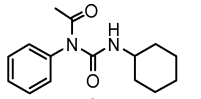
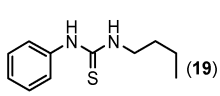
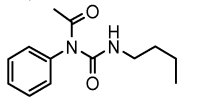
(14) Crystallographic data for compound **16a** have been deposited at the Cambridge Crysallographic Data Centre (deposition no. CCDC-669355). Copies of data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. [fax (int)] (01223 336033; email: deposit@ccdc.cam.ac.uk].

TABLE 1. N-Acylation of Ureas from Thioureas[a]

substrate	product[b]	yield (%)[c]
 (1)	 (1a)	92
 (2)	 (2a)	95
 (3)	 (3a)	96
 (4)	 (4a)	91
 (5)	 (5a)	72
 (6)	 (6a)	96
 (7)	 (7a)	70
 (8)	 (8a)	72
 (9)	 (9a)	65
 (10)	 (10a)	90
 (11)	 (11a)	00

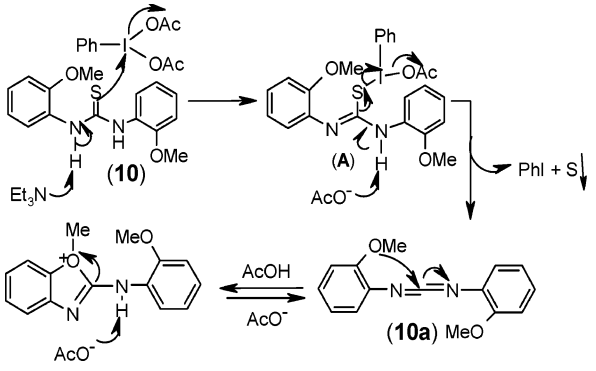
[a] Reactions were monitored by TLC. [b] Confirmed by IR and ^{1}H and ^{13}C NMR. [c] Isolated yield.

TABLE 2. Regioselective N-Acylation of Ureas from Thiourea

substrate	product[b]	yield (%)[c]
 (12)	 (12a) + (12b)	86 (3:2)
 (13) Cl	 (13a) + (13b) Cl	76 (3:2)
 (14) Br	 (14a) + (14b) Br	85 (2:1)
 (15)	 (15a)	82
 (16) O	 (16a) O	65
 (17) Ph	 (17a) Ph	65
 (18)	 (18a)	70
 (19)	 (19a)	50

[a] Reactions were monitored by TLC. [b] Confirmed by IR and ^{1}H and ^{13}C NMR. [c] Isolated yield.

SCHEME 4. Proposed Mechanism of Formation of Carbodiimide



lower than aniline (4.61); hence, the preferential N-acylation toward the *p*-chloro- and *p*-bromoaniline side in substrates **13** and **14** giving **13a** and **14a** as the major product as shown in Table 2. The exclusive regioselective formation of **15a** from unsymmetrical urea **15** is due to both the favorable pK_a and the steric factor of 2,6-dimethylaniline group. Regioselective N-acylation is also observed in thiourea **16**. The *N*-acylation toward the aniline side of **16** can be explained by the lower pK_a of the aniline compared to the *p*-anisidine (5.34), giving **16a** as the only isolable product. The structure of product **16a** has been confirmed by crystal X-ray crystallography.[14]

Again, the higher acidic character of the aromatic amine aniline compared to aliphatic amines such as benzylamine (pK_a 9.41), cyclohexylamine (pK_a 10.66), and *n*-butylamine (pK_a 10.77) indicates that the acylation is toward the aniline side of the urea as shown for substrates **17**, **18**, and **19** giving regioselective products **17a**, **18a**, and **19a**, respectively.

In conclusion, this paper reports an efficient method for the synthesis of N-acylated ureas from 1,3-disubstituted thioureas using environmentally benign reagent diacetoxy iodobenzene (DIB). For the first time, DIB has been employed as an acylating agent. We have also found the correlation between the regi-

oselectivity and the pK_a of the amine. Compared to the existing arduous methods of synthesis this methodology is superior in terms of environmental acceptability, simplicity, convenience, and general applicability.

Experimental Section

General Procedure for the Preparation of N-Acylated Urea (1a) from Thiourea (1). To a stirred solution of diphenylthiourea **1** (456 mg, 2 mmol) and triethylamine (276 μL, 2 mmol) in acetonitrile (10 mL) was added DIB (644 mg, 2 mmol) at room temperature, and the mixture was allowed to stir for 15 min. Precipitation of sulfur was observed during this period. After completion of the reaction, solvent was evaporated and admixed with ethyl acetate (20 mL). The ethyl acetate layer was washed subsequently with saturated solution of $NaHCO_3$ (5 mL) and 5% solution of sodium thiosulphate (5 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and purified over a silica gel column (hexane/EtOAc, 9:1) to give (419 mg, 92%) of the product **1a**. Compound **1a** was recrystallized from a mixture of EtOAc/hexane (8:2) to give a colorless crystal: mp 100−102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.98 (s, 3H), 7.08 (t, 1H, J = 7.2 Hz), 7.28 (m, 4H), 7.48 (m, 5H), 11.44 (s, 1H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 26.8, 120.3, 124.3, 129.1, 129.2, 129.3, 129.9, 137.8, 139.0, 152.1, 175.2; IR (KBr) 3230, 2928, 2857, 1722, 1668, 1602, 1544, 1492, 1445, 1166, 1050, 823, 751, 699 cm^{-1}; HRMS (ESI) MH$^+$ found 255.2946, $C_{15}H_{15}N_2O_2$ requires 255.2957.

Preparation of N-Propionylated Urea (1a′) from Thiourea (1). To a stirred solution of diphenylthiourea **1** (456 mg, 2 mmol), triethylamine (982 μL, 7 mmol), and propionic acid (374 μL, 5 mmol) in acetonitrile (10 mL) was added DIB (644 mg, 2 mmol) at room temperature, and the mixture was allowed to stir for 15 min. Precipitation of sulfur was observed during this period. After completion of the reaction, solvent was evaporated and admixed with ethyl acetate (20 mL). The ethyl acetate layer was washed subsequently with saturated solution of $NaHCO_3$ (5 mL) and 5% solution of sodium thiosulphate (5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. ^{1}H NMR analysis of the crude reaction mixture shows the formation of 1,3-diphenyl-1-propionylurea **1a′** and 1-acetyl-1,3-diphenylurea **1a** in a ratio of 83:17. Compound **1a′** was purified over a silica gel column (hexane/EtOAc, 9:1) to give (376 mg, 70%) of the product 1,3-diphenyl-1-propionylurea **1a′**. Compound **1a′** was recrystallized from a mixture of EtOAc/hexane (8:2) to give a colorless needle crystal: mp 114−115 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (t, 3H, J = 7.2 Hz), 2.18 (q, 2H, J = 7.2 Hz), 7.07−7.56 (m, 10H), 11.55 (s, 1H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 8.94, 31.6, 120.3, 124.2, 129.1, 129.2, 129.4, 129.9, 137.9, 138.3, 152.23, 178.4; IR (KBr) 3310, 2929, 1704, 1615, 1540, 1395, 1215, 1174, 1078, 899, 810, 753, 712 cm^{-1}; HRMS (ESI) MH$^+$, found 269.3235, $C_{15}H_{15}N_2O_2$ requires 269.3229.

Selected Spectral Data. 1-Acetyl-1,3-di-*p*-tolylurea (2a): mp 138−140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.03 (s, 3H), 2.35 (s, 3H), 2.45 (s, 3H), 7.10 (d, 2H, J = 8.0 Hz), 7.14 (d, 2H, J = 8.4 Hz), 7.22 (d, 2H, J = 8.4 Hz), 7.42 (d, 2H, J = 8.0 Hz), 11.35 (s, 1H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 20.9, 21.3, 26.7, 120.2, 128.8, 129.6, 130.5, 133.6, 135.3, 136.4, 139.1, 152.1, 175.2; IR (KBr) 3176, 3053, 2920, 2872, 1712, 1688, 1597, 1523, 1452, 1310, 1165, 813 cm^{-1}; HRMS (ESI) MH$^+$ found 283.3488, $C_{17}H_{19}N_2O_2$ requires 283.3493.

1-Acetyl-1,3-di-(*m*-methylphenyl)urea (3a): mp 82−84 °C; ^{1}H NMR (400 MHz $CDCl_3$) δ 2.00 (s, 3H), 2.31 (s, 3H), 2.40 (s, 3H), 6.90 (d, 1H, J = 7.2 Hz), 7.07 (d, 1H, J = 7.2 Hz), 7.08 (s, 1H), 7.17 (t, 1H, J = 7.6 Hz), 7.25 (d, 1H, J = 7.6 Hz), 7.29 (d, 1H, J = 8 Hz), 7.37 (t, 1H, J = 7.6 Hz), 7.46 (s, 1H), 11.40 (s, 1H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 21.3, 21.5, 26.5, 117.2, 120.8, 124.8, 125.9, 128.8, 129.5, 129.8, 137.7, 138.8, 139.8, 152.0, 175.0; IR (KBr) 3230, 3176, 1727, 1667, 1609, 1548, 1488, 1367, 1322, 1268, 1192, 1177, 1057, 794, 704, 690, 631 cm^{-1}; HRMS (ESI) MH$^+$ found 283.3490, $C_{17}H_{19}N_2O_2$ requires 283.3493.

1-Acetyl-1,3-di-(*o*,*p*-dimethylphenyl)urea (4a): mp 137−139 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.96 (s, 3H), 2.20 (s, 3H), 2.28 (s, 3H), 2.34 (s, 3H), 2.36 (s, 3H), 6.99 (m, 2H), 7.10 (m, 3H), 7.91 (d, 1H, J = 8 Hz), 11.27 (s, 1H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 17.7, 18.4, 21.1, 21.4, 26.3, 121.5, 127.4, 128.0, 128.4, 128.9, 131.2, 132.3, 133.8, 134.1, 135.6, 136.0, 139.5, 151.7, 175.6; IR (KBr) 3180, 2916, 1711, 1671, 1595, 1547, 1498, 1444, 1317, 1253, 1180, 1050, 965, 824, 725, 627, 506 cm^{-1}; HRMS (ESI) MH$^+$ found 311.4021, $C_{19}H_{23}N_2O_2$ requires 311.4029.

1-Acetyl-1,3-di-(*o*,*o*-dimethylphenyl)urea (5a): mp 109−111 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.93 (s, 3H), 2.26 (s, 6H), 2.31 (s, 6H), 7.05−7.26 (m, 6H), 10.67 (s, 1H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 18.0, 18.9, 25.3, 127.2, 128.3, 129.1, 129.2, 134.1, 135.4, 136.2, 137.3, 151.5, 175.4; IR (KBr) 3246, 2916, 1710, 1668, 1494, 1371, 1313, 1260, 1238, 1165, 1033, 777 cm^{-1}; HRMS (ESI) MH$^+$ HRMS (ESI) MH$^+$ found 311.4018, $C_{19}H_{23}N_2O_2$ requires 311.4029.

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Supporting Information Available: Experimental details and full characterization of compounds; IR, ^{1}H NMR, and ^{13}C NMR spectra. Crystallographic description (S2), ORTEP view (S3), and CIF files for compounds **1a** and **16a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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