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Note

A Facile Synthesis of N,N'-Disubstituted Ureas from Amide and Amine by Using N-Bromophthalimide (NBP) and Silveracetate in One Pot

Min-Soo Park and Chang-Uk Choi

College of Pharmacy, Kyungsung University, Pusan 608-736, Korea

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Various N,N'-disubstituted ureas **5** were easily prepared from the corresponding primary amide **1** by tratment with N-Bromophthalimide (NBP)-AgOAc-RNH_2 **4** in dry N,N-dimrthylformamide (DMF). This reaction envolved the intermediate formation of isocyanate **3** from amide **1** via Hofmann rearrangement by treatment with AgOAc and NBP and nucleophilic addition of amine **4** to this isocyante **3**. This method is simple enough to be applied to the synthesis of various N,N'-disubstututed ureas in large scale conviently.

Key words: N-Bromophthalimide, Isocyanate, Silveracetate, N,N'-Disubstituted urea

INTRODUCTION

Some N,N'-disubstituted ureas showed various biological activities. For example, siduron (Raymond,1963) is used as a herbcide, talinolol (Eckardt *et al.*, 1972) as an antihypertensive agent and 3,4,4'-trichlorocabanilide (Beaver *et al.*, 1957) showed an effective antibacterial activity as shown in Fig. 1.

Although many synthetic methods (Briody *et al.*, 1977; Yamashita *et al.*, 1976; Sandler and Karo, 1971) available for the N,N'-disubstituted ureas were developed, these methods have been limited in practical application to large scale synthesis due to their synthetic difficulties. As one of the simple synthetic methods for these ureas, addition of primary amine to isocyanate was recommended (March, 1992; Tagashi *et al.*, 1982; Stanovinik *et al.*, 1980). But this method also had some demerits that the isocyanate is too dangerous and unstable to handle in large scale. Therefore we tried developing practical synthetic method of N, N'-disubstituted ureas in connection with our developed Hofmann rearrangement, generating the isocyanate as intermediate. In our previous reports (Jew *et al.*, 1991; Park and Choi, 1993), we reported that treatment of primary amide with N-haloimidic compounds such as N-bromosuccinimide (NBS), dibromantin or N-bromophthalimide (NBP)-AgOAc-ROH provided the corresponding carbamates successfully. Based on this result, we convinced that the isocyanate was generated from primary amide as intermedeate in this reaction procedure, treating amide with N-bromoimidic compound and AgOAc, in an analogous mode of Hofmann rearrangement.

Perceiving the above fact that the isocyanate was generated from amide as intermedeate in our reaction procedure, we thought that N,N'-disubstituted ureas **5** could be obtained easily by nucleophilic addition of amine **4** to this isocyanate **3** as shown in Scheme 1.

In this paper we wish to report a new and practical synthetic method of N,N'-disubstituted ureas, treating amide **1** with NBP, AgOAc and amine **4**.

MATERIALS AND METHODS

All melting points were determined on an Electro thermal melting point apparatus and were uncorrected. IR spectra were taken on a Perkin-Elmer 683 infrared Spectrometer and are reported in cm^{-1} and ^1H NMR spectra were recorded on Brucker WP 80 and chemical shifts are reported in ppm (δ unit) from TMS as an internal standard and coupling constants are reported in Hz. N-Bromophthalimide was available from Aldrich chemical company and amides **1** were prepared from the corresponding carboxylic acid according to the literature (Shliner *et al.*, 1964).

N-Benzyl-N'-phenyl Urea (Typical reaction procedure)

Correspondence to: Min-Soo Park, College of Pharmacy, Kyungsung University, Pusan 608-736, Korea

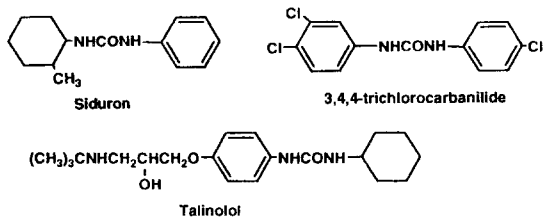
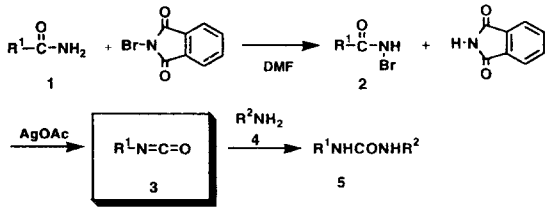


Fig. 1



Scheme 1

i) To a solution of phenylacetamide (100 mg, 0.73 mmol) and AgOAC (146 mg, 0.88 mmol) in dry DMF (10 ml), NBP (197 mg, 0.94 mmol) in 1.9 ml of dry DMF was added, and stirred at room temperature. After 0.5 hr, aniline (88 mg, 0.94 mmol) in 1 ml of dry DMF was added to this mixture, then stirred at room temperature under Ar atmosphere. After the reaction mixture was stirred for 8 hours, it was evaporated under reduced pressure; diluted with 100 ml of EtOAc; washed with H_2O (2×30 ml), 5% HCl (2×30 ml), saturated $NaHCO_3$ (2×30 ml) and saturated NaCl successively; dried over anhydrous $MgSO_4$; and evaported to give 178 mg of yellow solid, this was purified by column chromatography (silica gel, EtOAc) to give 150 mg of white solid (92%), mp. 155-158℃ IR (nujol) cm^{-1}: 3320, 1630; NMR ($CDCl_3$) δ: 4,42 (d, 2H, CH_2NH, J= 6.0 Hz), 7.00-7.30 (m, 5H, 5×Ar-H), 7.29 (s, 5H, 5×Ar-H).

ii) To a solution of benzamide (100 mg, 0.82 mmol) and AgOAc (160 mg, 0.98 mmol) in dry DMF (10 ml), NBP (241 mg, 1.03 mmol) in 2.4 ml DMF was added, and stirred at room temperature. After 0.5 hr benzylamine (105 mg, 0.98 mmol) in 1 ml DMF was added to this reaction mixture and stirred at room temperature under Ar atmosphere. After 9 hours, it was worked up and purified as in the preceding experiment to give white solid (155 mg, 84%). This compound showed the same Rf value in tlc and spectral data in I.R and NMR as the obtained compound in the above experiment.

N,N'-Diphenyl Urea

To a solution of benzamide (100 mg, 0.82 mmol) and AgOAc (160 mg, 0.98 mmol) in dry DMF (10 ml), NBP (241 mg, 1.03 mmol) in 2.4 ml DMF was added to this reaction mixture and stirred at room temperature. After 0.5 hours, aniline (91 mg, 0.98 mmol) in 1 ml DMF was added to this reaction mixture and stirred at room temperature under Ar atmosphere. After 9 hours, the reaction mixture was worked up and purified as in the preceding experiment to afford white solid (150 mg, 89%). mp. 216-219℃ [lit.(Dieck *et al.*), 233-235℃]: IR (nujol) cm^{-1}; 3320, 1620: NMR ($CDCl_3$) δ; 7.09-7.38 (m, 10H, 10×Ar-H).

N-Cyclohexyl-N'-phenyl Urea

i) The same experimental procedure as in the typical procedure was applied to the reaction of cyclohexanamide (100 mg, 0.78 mmol), AgOAc (156 mg, 0.94 mmol), NBP (229 mg, 1.03 mmol) and aniline (96 mg, 1.03 mmol) to afford 156 mg of white solid (89%). mp. 148-153° [lit. (Wolman and Gallop, 1962), 150° C]: IR (nujol) cm^{-1}; 3320, 1620 : NMR ($CDCl_3$) δ; 0.90-2.04 (m, 10H, 5×CH_2) 3.66 (br, 1H, CHNH), 7.06-7.32 (m, 5H, 5×Ar-H).

ii) The same experimental procedure as in the typical procedure was applied to the reaction of benzamide (100 mg, 0.82 mmol), AgOAc (160 mg, 0.98 mmol), NBP (241 mg, 1.03 mmol) and cyclohexylamine (97 mg, 0.98 mmol) to give 145 mg of white solid (81%) N,N'-Dicyclohexylurea The same experimental procedure as in the typical procedure was applied to the reaction of cyclohexanamide (100 mg, 0.78 mmol), AgOAc (156 mg, 0.94 mmol), NBP (229 mg, 1.03 mmol) and cyclohexylamine (93 mg, 0.94 mmol) to afford 140 mg of white solid (79 %). mp. 223℃ [lit. (Acott *et al.*, 1968), 230-231℃]: IR (nujol) cm^{-1}; 3320, 1620: NMR ($CDCl_3$) δ; 1.20-2.10 (m, 20H, 10×CH_2), 3,60 (m, 2H, CH-NH).

N-Heptyl-N'-phenyl Urea

The same experimental procedure as in the typical procedure was applied to the reaction of octanamide (100 mg, 0.70 mmol), AgOAc (140 mg, 0.84 mmol), NBP (206 mg, 0.91mmol) and aniline (85 mg, 0.91 mmol) to give 191 mg of semi solid (82%). IR; (neat) cm^{-1}; 3360, 1630: NMR ($CDCl_3$) δ; 0.80 (t, 3H, CH_3, J=6.0 Hz), 1.20-1.70 (m, 10H, 5×CH_2), 3.26 (m, 2H, CH_2-NH), 7.00-7.30 (m, 5H, 5×Ar-H).

N-Pentyl-N'-phenyl Urea

The same experimental procedure as in the typical procedure was applied to the reaction of hexanamide (100mg, 0.86 mmol), AgOAc (172 mg, 1.03 mmol), NBP (233 mg, 1.24 mmol) and aniline (115 mg, 1.03 mmol) to afford 155 mg of semisolid (87%). IR; (nujol) cm^{-1}; 3360, 1630 : NMR ($CDCl_3$) δ; 0.80 (t, 3H, CH_3, J=6.0 Hz), 1.20-1.65 (m, 6H, 3×CH_2), 3.06 (2H, CH_2-NH), 6.90-7.20 (m, 5H, 5×Ar-H).

Table I. The conversion of primary amides **1** to N,N'-disubstituted urea **5**

R^1CONH_2 (**1**) $\xrightarrow{AgOAc/NBP/R^2NH_2\ \mathbf{4}/DMF}$ $R^1NHCONHR^2$ (**5**)

R^1(**1**)	R^2(**4**)	Yields of **5** (%)
$C_6H_5CH_2$	C_6H_5	92
C_6H_5	$C_6H_5CH_2$	84
C_6H_5	C_6H_5	89
C_6H_5	cyclohexyl	81
cyclohexyl	C_6H_5	89
cyclohexyl	cyclohexyl	79
C_7H_{15}	C_6H_5	82
C_5H_{11}	C_6H_5	87

RESULTS AND DISCUSSION

As shown in experimental section, a series of primary amides **1** was converted to the corresponding N,N'-disubstituted ureas **5** in good yields by treatment with NBP-AgOAc-R^2NH_2 **4**. And the results were summarized in Table 1.

In our preliminary experiment, aniline was immediately added to the reaction mixture of phenylactamide, silveracetate and NBP. But in this reaction procedure, most of the phenylacetamide, the starting material, remained unreacted after stirring for 9 hours. Based on this result, we thought that the bomonium ion (or its equivalent), generated from NBP, was first attacked by the amine instead of amide, because the amine is more nucleophilic than amide. So the N-bromination of amide, the first step in this reaction, could not occur. Therefore at the next trial, aniline was added slowly after stirring until the color of the reaction mixture of amide, silveracetate and NBP turned a little gray (about 30 minutes). The gray color was thought to indicate the formation of AgBr, resulted from the Hofmann rearrangement. In this case, we could obtained the intended N-benzyl-N'-phenyl urea in 92% yield as described in experimental section. So we performed the reaction for various amides **1** and amines **4** in a similar reaction procedure.

As shown in Table 1, various N,N'-disubstituted ureas **5** could be obtained from the corresponding amide **1** in excellent yields in one pot by this method. From the results, it is conceivable that the N,N'-disubstituted ureas were produced by rapid nucleophilic addition of amine **4** to the isocyanate **3**, generated in situ in our reaction condition.

As an excellent method for the preparation of N,N'-disubstituted urea, addition of amine to isocyanate was recomended (March, 1992). But this method has some troubles that the isocyanate is too dangerous and unstable to handle in large scale. However in our synthetic method, such shortcomings can be overcome because rapid nucleophilic addition of amine **4** to the isocyante **3**, generated in situ, is occured to give urea **5** in one pot.

From the foregoing discussion, we think that our method is so efficient that this can be applied to the synthesis of various useful N,N'-disubstituted ureas conviently.

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