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The modified 'phosphine imide' reaction: a safe and soft alternative ureas synthesis

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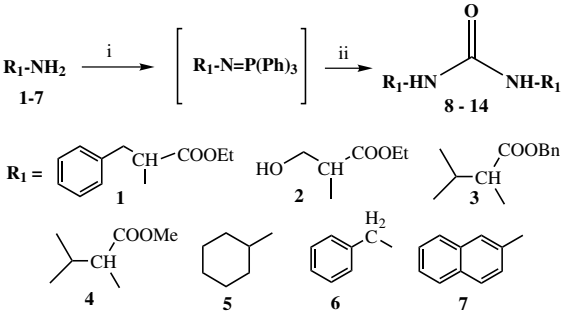
Abstract—In this work we present a new way for the direct and general synthesis of urea compounds from primary amines by the modified 'phosphine imide' reaction. A large panel of amine structures are compatible with the smooth reaction conditions. Particularly in the case of sensitive L-aminoesters, it is interesting to note that the stereochemistry at the asymmetric centre was unmodified in the reaction conditions.

It is obvious that new methods and strategies leading to the efficient formation of amide or urea bonds remain very important in peptide or pseudopeptide synthesis.[1] An interesting approach earlier reported in the literature described a first one-step modified reaction enabling the obtention of isocyanates from primary amines and phenylalanine methyl ester using the Mitsunobu chemistry.[2] Very recently, the so-called 'phosphine imide' strategy has been intensively employed to achieve simple and direct access to sophisticated cyclodextrin host derivatives (including preparation of Cds monoisocyanate), via the formation of urea or thiourea bonds from azides.[3]

In the present work, the extension of the latter to primary amines or L-aminoacid esters in place of azides is proposed. As demonstrated earlier by Appel,[4] we suggest a new approach, which combines an amino phosphonium salt step formation obtained by the reaction of an amine with the triphenylphosphine/CCl_4 reagent, then followed by its in situ base dehydrohalogenation. This should give an iminophosphorane intermediate (Scheme 1) and will finally be able to give, through the phosphine imide route, the expected ureido derivatives.[5]



Scheme 1. Reagents and conditions: (i) $CCl_4/P(Ph)_3/Et_3N/CH_2Cl_2/Ar$; (ii) R1-$NH_2$ (1 equiv)/CO_2/24 h/rt.

As previously reported in the case of the phosphine imide reaction,[3] the new synthesis presented here could also run in a 'one-pot' manner.[7] As illustrated in Scheme 1, pseudoureido dipeptide esters **8**–**11** and bis-ureas **12**–**14** are obtained in medium to good yields (see Table 1) from L-aminoacid esters **1**–**4** and primary amines **5**–**7** by reaction with: triphenylphosphine/CCl_4, Et_3N, then 24 h, rt, CO_2 bubbling in anhydrous CH_2Cl_2 or DMF. However, the reaction with less reactive aromatic amines, for example, naphthylamine **7** works poorly and a large amount of the starting product was recovered.[8] The spectroscopic data[6] are in perfect agreement with the proposed structures. It is interesting to point out that no racemization occurs at the asymmetric centre of L-aminoacid esters as confirmed by ^1H- and ^{13}C NMR.

Keywords: Urea formation; Modified phosphine imide reaction.
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Table 1. Pseudoureido dipeptide derivatives and ureas **8–14**

Amine		Urea	Yield (%)
1	L-Phenylalanine ethylester[a]	**8**	89
2	L-Serine ethylester[b]	**9**	41
3	L-Valine benzylester[c]	**10**	47
4	L-Valine methylester[c]	**11**	65
5	Cyclohexylamine[d]	**12**	96
6	Benzylamine[d]	**13**	79
7	Naphtylamine[d]	**14**	17

[a] Conditions: amine (mmol) = 8, $P(Ph)_3$ (equiv) = 1.2, CCl_4 (equiv) = 0.6; Et_3N = 3 mL.
[b] Conditions: amine (mmol) = 5.1, $P(Ph)_3$ (equiv) = 5.7, CCl_4 (equiv) = 2.8, Et_3N = 1.5 mL.
[c] Conditions: amine (mmol) = 6, $P(Ph)_3$ (equiv) = 6.6, CCl_4 (equiv) = 0.6; Et_3N = 3 mL.
[d] Conditions: amine (mmol) = 8, $P(Ph)_3$ (equiv) = 1.1, CCl_4 (equiv) = 1.1; Et_3N = 3 mL.

Moreover, the primary alcohol side group in L-serine, needs no protection and remains unchanged in the reaction conditions.

In conclusion, we have shown the in situ modified 'phosphine imide' reaction could be applied successfully to primary amines in place of azides in a 'one-pot' procedure to afford symmetrical ureas. We argued this method could be also considered as a valuable alternative to recently described methods, for example, obtention of ureas using Mitsunobu reagent, or hazardous phosgene or triphosgene.[9] Future work to apply the reaction to dissymmetric ureas and in the solid phase to free aminoacids or, for example, to protected peptides intermolecular coupling is under investigation.

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6. Structure of all compounds were assigned by ^1H and ^{13}C NMR on a Bruker-DRX 400 spectrometer, FTIR spectra were recorded on a Bruker–Vector 22 spectrometer. The solvents were purified by standard methods.
7. Ureas **8–11**. Carbon tetrachloride (0.6 equiv) was added to a mixture of triphenylphosphine (1.1 equiv) and amine (1 equiv) in anhydrous CH_2Cl_2. The mixture was stirred and heated at reflux under argon for 24 h. The solution was concentrated to dryness. Anhydrous CH_2Cl_2 was added to the residue. Then triethylamine (1 equiv) was added to the solution and the mixture was stirred 2 h at rt. After, the mixture was stirred at rt under CO_2 for 24 h more. The solution was concentrated to dryness and the residue was chromatographed on a silica gel column.
N,*N*′-2-[Di-(phenylethylpropanoate)]-urea **8**. Yield (%) 89 (3.8 mmol, 1.58 g); TLC SiO_2; CH_2Cl_2/MeOH 93/7; R_f = 0.34; IR (KBr) ν = 3357 (NH); 1625 (NH–*C*=*O*); ^1H NMR (CD_3OD) δ = 1.23 (t, CH_3, J = 6.9 Hz); 3.03 (d, 4H, CH_2Bn, J = 5.7 Hz); 4.12 (m, 4H, CH_2); 4.79 (m, 2H,CH); 5.26 (m, 2H, NH); 7.11–7.28 (10H, *arom*); ^{13}C NMR (CD_3OD) = 14.0 (CH_3); 38.72 (CH_2Bn); 54.0 (CH); 61.28 (CH_2–CH_3); 126.8 (C_4 *arom*); 128.3 (C_3 *arom*); 129.4 (C_2 *arom*); 136.2 (C_1 arom); 156.2 (NH–C=O); 172.8 (O–C=O). ESI-MS m/z (%) = 413.3 (100) $[M+H]^+$.
N,*N*′-2-[Di-(methyl-2-hydroxymethylethanoate)]-urea **9**. Yield (%) 41 (2.43 mmol, 0.324 g); TLC (SiO_2; AcOEt/MeOH 4/1); R_f = 0.27; IR (KBr) ν = 3100–3500 (OH); 1735 (NH–C=O); ^1H NMR (DMSO) δ = 1.11 (t, 6H, CH_3, J = 7.05 Hz); 3.57 (d, 4H, CH_2, J = 7.05 Hz); 4.12 (m, 4H, CH–CH_3); 3.76 (m, 2H, CH); 3.88 (m, 4H, CH_2–OH); ^{13}C NMR (DMSO) δ = 17.2 (CH_3); 57.7 (CH_2); 60.5 (CH); 63.2 (CH_2OH); 168.5 (O–C=O); 172.5 (NH–C=O).
N,*N*′-2-[Di-(benzylisopentanoate)]-urea **10**. Yield (%) 47 (2.82 mmol, 0.584 g); TLC (SiO_2; AcOEt/hexane/CH_2Cl_2 1/1/1); R_f = 0.80; IR (KBr) ν = 3332 (NH); 1740 (NH–C=O); ^1H NMR ($CDCl_3$) δ = 0.89 (d, 6H, CH_3, J = 6.9 Hz); 0.95 (d, 6H, CH_3, J = 6.9 Hz); 2.15 (m, 2H, $CH(CH_3)_2$); 4.51 (dd, 2H, CH, J = 4.6 Hz, J = 8.8 Hz); 5.19 (dd, 2H, NH, J = 12.2 Hz, J = 37.2 Hz); 7.32–7.39 (m, 8H, *arom*); ^{13}C NMR ($CDCl_3$) δ = 17.9 (CH_3); 19.5 (CH_3); 31.9 ($CH(CH_3)_2$); 58.4 (CH); 67.4 (C_1 *arom*); 128.7 (C_3 *arom*); 128.9 (C_2 *arom*); 135.8 (C_4 *arom*); 157.9 (O–C=O); 173.97(NH–C=O).
N,*N*′-2-[Di-(methylisopentanoate)]-urea **11**. Yield (%) 65 (3.89 mmol, 1.12 g); TLC (SiO_2; CH_2Cl_2/AcOEt/MeOH/hexane2/1/1/1); R_f = 0.50; IR (KBr) ν = 3382 (NH); 1736 (NH–C=O); ^1H NMR ($CDCl_3$) δ = 0.9 (6H, d, CH_3, J = 6.9 Hz); 2.21 (m, 2H, $CH(CH_3)_2$); 2.96 (s, 2H, NH); 3.31 (dd, 2H, CH, J = 4.6 Hz, J = 8.8 Hz); 3.74 (m, 6H, CH_3); ^{13}C NMR ($CDCl_3$) δ = 17.6 (C_3); 19.6 (C_3); 32.6 ($CH(CH_3)_2$); 52.1 (CH); 60.4 (CH_3); 162.9 (O–C=O); 176.4 (NH–C=O).
8. Ureas **12–14**. Carbon tetrachloride (0.88 mL; 1.1 equiv) was added to a mixture of triphenylphosphine (2.26 g, 1.1 equiv) and corresponding amine (1 equiv) in anhydrous CH_2Cl_2 (20 mL/mmol of amine). The mixture was stirred and heated at reflux under argon for 24 h. The solution was concentrated to dryness. Anhydrous CH_2Cl_2 was added to the residue with triethylamine (1 equiv) and the mixture was stirred at rt. After 2 h, amine (1 equiv) was added and the mixture was stirred at rt under CO_2 for 24 h. The solution was concentrated to dryness and mixture of diethylether and water (3:1) was added to the residue at 0 °C. The resulting precipitate was filtered and washed thoroughly with diethylether and cold water.

N,*N*′-Dicyclohexylurea **12**. Yield (%) 96 (7.1 mmol, 1.59 g); mp = 233–234 °C; IR (KBr) $v = 3328$ (NH); 1655 (N–C=O); ^{1}H NMR (CF_3COOD) $\delta = 3.50$ (2H, m, CH–CH_2–); 2.20–1.00 (m, 20H, –CH_2–); ^{13}C NMR ($CDCl_3$) $\delta = 25.3$ (C_4); 26.0 (C_3); 34.3 (C_2); 49.7 (C_1); 155.0 (NH–C=O).

N,*N*′-Dibenzylurea **13**. Yield (%) 79 (6.3 mmol, 1.52 g); mp = 170–171 °C; TLC (SiO_2; CH_2Cl_2/MeOH 96/4); $R_f = 0.34$; IR (KBr) $v = 3323$ (NH); 1627 (NH–C=O); ^{1}H NMR ($CDCl_3$) $\delta = 4.24$ (d, 4H, CH_2, $J = 5.91$ Hz); 6.43 (t, 2H, NH, $J = 5.8$ Hz); 7.20–7.38 (m, 8H, *arom*); ^{13}C NMR ($CDCl_3$) $\delta = 43.9$ (CH_2); 127.4 (C_4 *arom*); 127.9 (C_2 *arom*); 129.1 (C_3 *arom*); 141.8 (C_1 *arom*); 158.9 (N–C=O).

N,*N*′-Dinaphtylurea **14**. Yield (%) 17 (1.4 mmol, 0.430 g); mp = 275–280 °C decomposition; IR (KBr) $v = 3377$ (NH); 1637 (NH–C=O); ^{1}H NMR ($CDCl_3$) $\delta = 5.31$ (2H, s, NH); 7.48–7.96 (m, 14H, *arom*).

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