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Reaction Mechanisms

O-Phenylisourea Synthesis and Deprotonation: Carbodiimide Elimination Precludes the Reported Chapman Rearrangement

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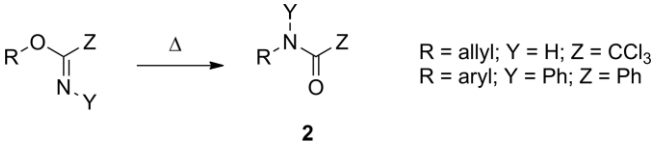
Abstract: The kinetics of the addition of phenol to diisopropylcarbodiimide, and reaction of the resulting *N*,*N*′-diisopropyl-*O*-phenylisourea with hydroxide, are reported. The isourea is generated by a slow overall termolecular equilibrium process, inhibited by isourea–phenol salt generation. In contrast to an earlier report, reaction of the isourea with hydroxide does not induce a synthetically useful 1,3-O–N (Chapman) rearrangement. Instead, deprotonation results in solvolysis by carbodiimide elimination.

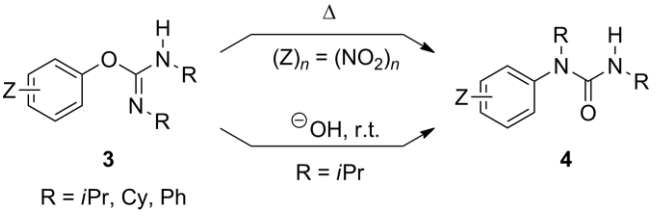
Introduction

The direct,[1] or catalysed[2] 1,3-O–N rearrangement of imidates (**1**) to amides (**2**) has been substantially developed (Scheme 1). The Chapman rearrangement (**1** → **2**; R = Ar)[3] provides a synthetic route to aniline derivatives from readily available phenols. However, this process has been far less developed than the analogous rearrangement where R = allyl.[1,2]



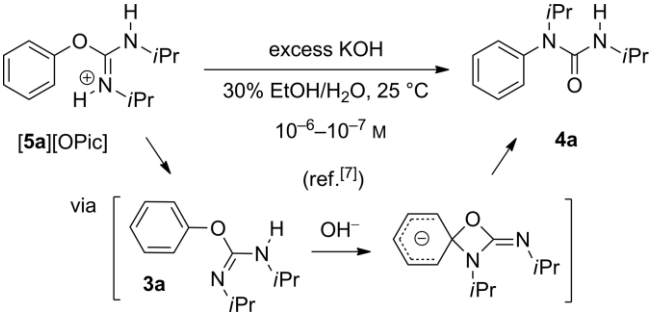
Scheme 1. Thermal 1,3-O–N rearrangement of imidates **1** to amides **2**; known as the Chapman rearrangement when R = Ar.

The Chapman rearrangement proceeds by intramolecular generation of a zwitterionic Meisenheimer-like transition state or intermediate.[4] Although this process is accelerated by aryl groups bearing electron-withdrawing substituent(s), in nearly all cases the Chapman rearrangement of *O*-arylimidates (R = Ar; Y/Z = Ar′; Scheme 1) requires high temperatures (200–300 °C) to effect useful conversions.[3,4] The analogous thermal 1,3-O–N rearrangement of *O*-arylisoureas (**3** → **4**; Scheme 2) has also been reported, but only with examples where Ar is (poly)-nitrated and thus highly electron-deficient.[5] Less strongly activated systems resist rearrangement.[6] In 1983, Suttle and Williams reported that the isourea rearrangement is catalysed by hydroxide, at ambient temperature, even with relatively neutral aryl substituents (Z; Scheme 2).[7]



Scheme 2. Rearrangement of *O*-arylisoureas **3** to *N*-arylureas **4**. Top: thermal rearrangement (only when Z is strongly electron-withdrawing). Bottom: base-catalysed rearrangement, reported to proceed with a wide range of Z.[7]

The overall second-order kinetics were found to correlate with the pK_{aH} of the corresponding phenol, and a mechanism involving equilibrium N–H deprotonation of **3**, followed by rate-limiting intramolecular rearrangement (Z = H; $\Delta S^{\ddagger}$ = –13.4 cal K^{-1} mol^{-1}) was proposed (Scheme 3). Given that a broad substrate scope rearrangement would provide substantial sythetic utility, we were surprised to find there have been no reported applications.[8] We initially suspected that this was due to the reported use of potentially hazardous[9] picrate salts ([**5**][OPic]), prepared by fusion of the phenol with diisopropylcarbodiimide (**6a**), then addition to a cold picric acid solution. The isoureas were liberated in situ for rearrangement ([**5**][OPic] → **3** → **4**).[7]



Scheme 3. Reported deprotonation/rearrangement of isourea **3a**, liberated in situ from [**5a**][OPic]; OPic = [2,4,6-$(O_2N)_3C_6H_2O^-$].[7]

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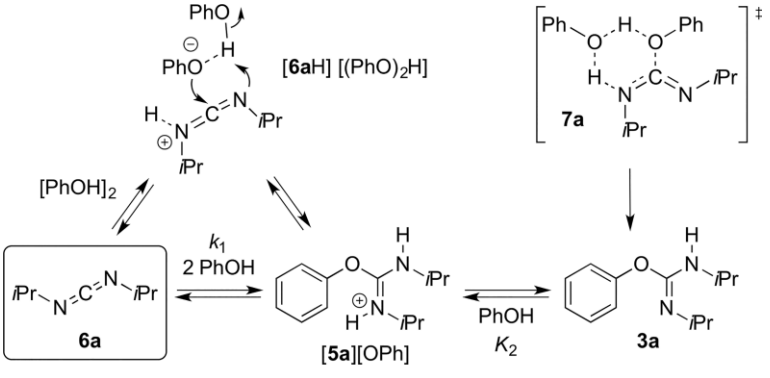
We have now re-investigated the process[7] in some detail and herein report on (a) the generation of *O*-phenylisourea **3a** from PhOH and diisopropylcarbodiimide (**6a**), and (b) the reaction of [**5a**][OPic] and related salts with excess base. We show why the kinetics for direct generation of isourea **3a** from PhOH and **6a** is synthetically disadvantageous. Moreover, we show that *O*-phenylisourea **3a** does not rearrange under the reported conditions[7] but instead undergoes elimination and solvolysis.

Results and Discussion

Synthesis of *O*-Phenylisourea 3a

The preparation of a range of *O*-arylisoureas from phenols (ArOH) and carbodiimides has been documented.[10] Most procedures use an excess of the phenol, but common to all is the use of high reaction concentrations (usually by fusion of neat reactants) at high temperatures. To the best of our knowledge, the mechanistic origins for the requirement of such conditions have not been elucidated.[10] The kinetics of the reaction of diisopropylcarbodiimide (**6a**; 0.24 M) with PhOH (0.25 M) in $CDCl_3$ at 21 °C was studied in situ by ^1H NMR spectroscopy; see data (A) in Figure 1.

The overall reaction involves the slow attainment of an equilibrium mixture of product **3a** and reactants. However, this occurs by a two-stage process, the second stage being many orders of magnitude slower than the first one. In the first stage of the reaction (up to 50 % conversion of **6a**) the major product is not the isourea (**3a**), but the salt [**5a**][OPh]. As a consequence, the reaction becomes extremely slow as the PhOH concentration is almost completely depleted. Accordingly, introduction of further **6a** at this point has minor impact on the rate (B; Figure 1). In contrast, introduction of a second equivalent of PhOH induces further conversion (C; Figure 1). The kinetics can be satisfactorily simulated (see solid lines through datasets A, B, C; Figure 1) by an overall third-order initial reaction: $-d[\mathbf{6a}]/dt = k_{obs}[PhOH]^2[\mathbf{6a}]$. This is consistent with two phenol molecules adding to carbodimide (**6a**), either stepwise, e.g. via [**6a**H][$(PhO)_2$H] to directly generate the salt [**5a**][OPh], or in a concerted manner, e.g. reaction of a phenol dimer with **6a** to generate **3a**, via **7a**. In either pathway, the overall third-order kinetics, exacerbated by phenol sequestration through salt formation account for the forcing conditions.[7,11]



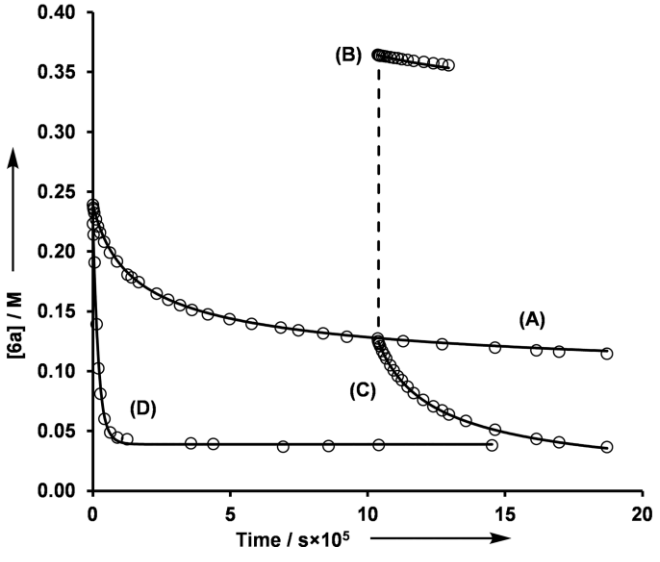
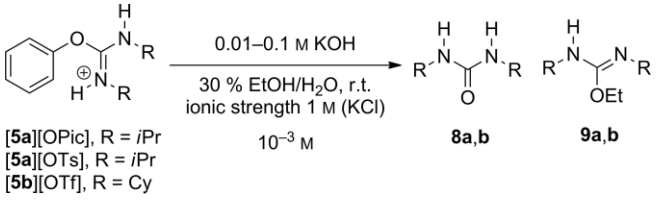


Figure 1. Temporal concentration of [**6a**] during the reaction with PhOH (0.25 M) in $CDCl_3$, 21 °C. Open circles: data (in situ ^1H NMR); solid lines: simulation according to model shown; $k_1 = 6.2 \times 10^{-5}$ M^{-2} s^{-1}; $K_1 = 2 \times 10^3$ M^{-2}; $K_2 = 63$ M^{-1}; (A) standard reaction; (B) additional **6a** (0.24 M) added at point indicated; (C) additional PhOH (0.25 M) added; (D) full equilibrium for standard conditions (as A) attained by catalysis (20 mol-% CuCl; sparingly soluble).

Reaction of *O*-Phenylisourea Salts with KOH

Reaction of PhOH with diisopropyl- (**6a**) or dicyclohexylcarbodiimide (**6b**), followed by silica-gel adsorption, extraction of residual **6a**,**b** and PhOH, elution with diethyl ether, concentration, and trituration, gave crude isoureas **3a**,**b**. A variety of isourea salts were prepared by addition of the corresponding acids. Those most amenable to handling (crystalline, non-hygroscopic) were found to be [**5a**][OTs] and [**5b**][OTf]. For reasons of safety,[9] we did not initially prepare samples of the picrate salt [**5a**][OPic].[7]

The isourea rearrangement (**3** → **4**) reported by Suttle and Williams[7] employed low concentrations of [**5a**][OPic] (10^{-6} to 10^{-7} M, in 30 % EtOH/H_2O), at unspecified KOH concentrations. The product (**4a**) having been identified by HPLC and UV analyses, was referenced against independently prepared samples.[7] In initial reactions we employed [**5a**][OTs] (10^{-3} M, in 30 % EtOH/H_2O) and tested for rearrangement on addition of 0.1 and 0.01 M KOH. However, no trace of **4a** could be detected [≤ 10^{-5} M (1 %)]. Instead, the reaction mixture consisted solely of solvolysis products (Scheme 4) identified (NMR, MS, IR) as PhOH, *N*,*N*′-diisopropylurea **8a** (major) and the transesterified isourea **9a** (minor). Analogously, [**5b**][OTf] gave **8b**/**9b**, and no **4b**.



Scheme 4. Reaction of salts [**5a**] and [**5b**] with KOH to give *N*,*N*′-dialkylureas **8a**,**b** plus small amounts (6–8 %) of the isourea ethanolysis product (**9a,b**). No trace of **4a**,**b** was detected by ^{1}H NMR analysis (detection threshold ca. 1 %).

At this stage we suspected that either the presence of picrate ions is essential for the rearrangement (**3** → **4**),[7] for example to facilitate an electron-transfer process, or that intermolecular association of the isourea (e.g. as an H-bond dimer)[12] may be diverting $(\mathbf{3a})_n$ towards solvolysis. However, addition of picric acid (10^{-3} M) had no impact on the outcome, nor did conduct-

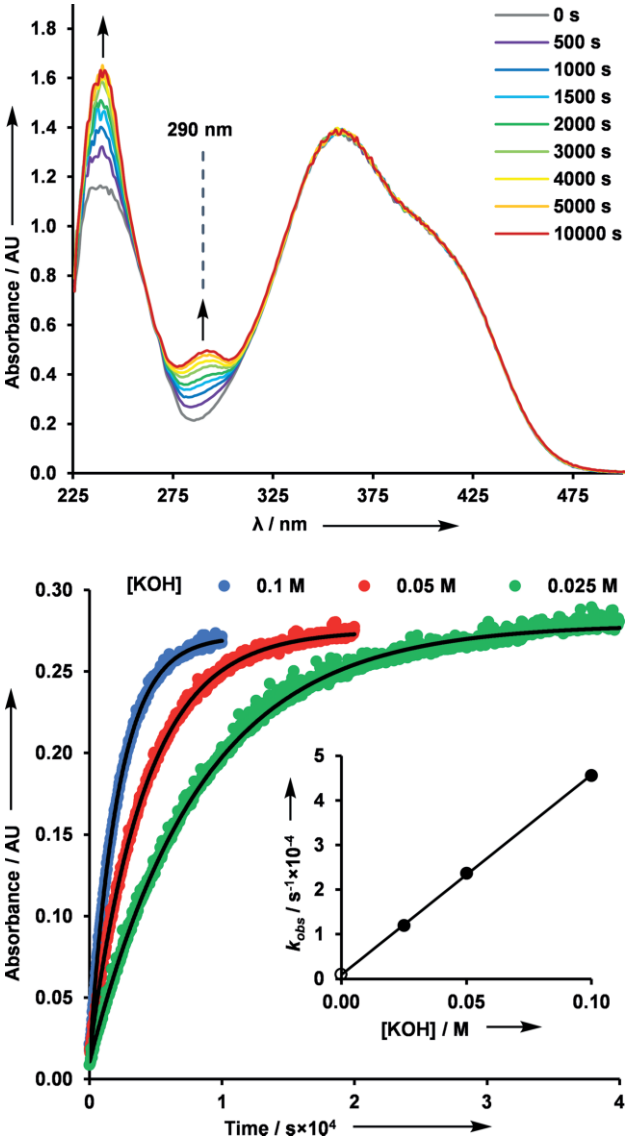


Figure 2. Top: selected UV spectra showing key changes in the absorbance (*A*) centred at 242 and 290 nm during the reaction of [**5a**][OPic] (10^{-4} M) with KOH (0.1 M) in 30 % EtOH/H_2O at 25 °C. Bottom: kinetics determined at 290 nm, initial [**5a**][OTs] concentration 10^{-4} M, path length 1 cm. Data: closed circles; fit: $A = ae^{-kt} + b$, where *a* and *b* are fitting parameters, and $k = k_{obs}$ [s^{-1}]. Inset: first-order dependence on KOH; $-d[\mathbf{3a}]/dt = [\mathbf{3a}](k_{OH}[OH] + k_0)$; $k_{OH} = 4.48 \times 10^{-3}$ M^{-1} s^{-1}. The uncatalysed reaction is slow: $k_0 \leq 0.9 \times 10^{-5}$ s^{-1}.

Table 1. Solvolysis rate constants for **3a**,**b** (KOH in 30 % EtOH/H_2O, 25 °C).

Entry	Salt	Conc.[a] [M]	[KOH][b] [M]	k_{obs}[c] [s^{-1}]	k_{OH}[d] [M^{-1} s^{-1}]
1	[**5a**][OPic]	1×10^{-4}	1.0×10^{-1}	4.6×10^{-4}	4.6×10^{-3}
2	[**5a**][OPic]	1×10^{-5}	1.0×10^{-1}	4.1×10^{-4}	4.1×10^{-3}
3[e]	[**5a**][OPic]	–[f]	–[g]	–[g]	5.7×10^{-3}[e]
4	[**5a**][OTs]	1×10^{-4}	1.0×10^{-1}	4.6×10^{-4}	4.6×10^{-3}
5	[**5a**][OTs]	1×10^{-5}	1.0×10^{-1}	4.9×10^{-4}	4.9×10^{-3}
6	[**5b**][OTf]	1×10^{-4}	1.0×10^{-1}	4.1×10^{-4}	4.1×10^{-3}
7	[**5b**][OTf]	1×10^{-5}	1.0×10^{-1}	3.9×10^{-4}	3.9×10^{-3}
8	[**5a**][OTs]	1×10^{-4}	5.0×10^{-2}	2.4×10^{-4}	4.8×10^{-3}
9	[**5a**][OTs]	1×10^{-4}	2.5×10^{-2}	1.2×10^{-4}	4.8×10^{-3}
10[h]	[**5a**][OTs]	1×10^{-4}	1.0×10^{-1}	1.1×10^{-3}	1.1×10^{-2}[i]

[a] *O*-Arylisourea **3** liberated in situ from the salt. The product is a mixture (approximately 13:1) of **8**/**9**. [b] Ionic strength 1.0 M (KOH/KCl). [c] Empirical pseudo first-order rate constant (UV; 290 nm). [d] Second-order rate constant. [e] From ref.[7]; product is reported as **4a**. [f] 10^{-6} to 10^{-7}. [g] Not specified. [h] Reaction in 30 % EtOD/D_2O. [i] Solvent kinetic isotope effect (KIE) = 0.42.

ing the reaction at a 100-fold dilution (10^{-5} M), or using the pure picrate salt [**5a**][OPic]. Rather perplexed, we measured the rates of solvolysis (**3** → **8/9**) to compare with the kinetic data reported for the rearrangement (**3** → **4**).[7] Suttle and Williams determined reaction rates by UV spectroscopy, monitoring the temporal change in absorption (*A*) at 290 nm.[7] As shown in Figure 2 (top), the reaction of [**5a**][OPic] (10^{-4} M) with 0.1 M KOH did indeed give temporal changes centred at 242 and 290 nm. However, the reaction products, identified by NMR spectroscopy, were still **8a**/**9a** (as Scheme 4).

Curve fitting of *A* (λ = 290 nm) vs. *t*, gave k_{obs} [s^{-1}] (Table 1, Entry 1). The same empirical rate constant, within experimental error, was obtained at lower substrate concentration (10^{-5} M; Entry 2) and with [**5a**][OTs] (Entries 4 and 5; lower section of Figure 2). The cyclohexyl system ([**5b**][OTf]) reacted at a very similar rate (Entries 6 and 7). Reactions of [**5a**][OTs] conducted at lower [KOH] concentrations but at the same ionic strength (Entries 8 and 9) confirmed that the reaction is first order in KOH (inset; Figure 2), allowing extraction of the second-order rate constants (k_{OH}; Table 1). All of the reactions led to solvolysis, not rearrangement.

Mechanism of Solvolysis

To investigate whether the solvolysis of **3a** proceeds by an addition/elimination or an elimination/addition mechanism, the reaction of [**5a**][OTs] with KOD was monitored by ^{1}H NMR spectroscopy in 30 % [D_6]EtOD/D_2O. Deprotonation of the salt (k_1) to generate **3a** was instantaneous, after which two distinct steps for the conversion of **3a** into **8a**/**9a** (in constant ratio) were identified: elimination of phenolate, followed by slow solvolysis of the resulting carbodiimide **6a** (Figure 3).

The kinetics was satisfactorily simulated by inclusion of base-catalysed solvolysis ($k_3 + k_4$) of **6a** and an inverse solvent kinetic isotope effect (k_D/k_H = 2.4) for the elimination (k_2), confirmed by UV (Table 1, Entry 10). The solvolysis of diisopropylcarbodiimide **6a** in 30 % [D_6]EtOD/D_2O was measured independently by ^{1}H NMR, see inset to Figure 4, confirming hydroxide catalysis ($k_{obs} = k_{OR}$[KOD]; where $k_{OR} = k_3 + k_4$). The inverse isotope effect for phenolate elimination is indicative that deprotonation of N–H/D in **3a** is not rate-limiting (E2), but is consistent with that expected[13] for an E1cb mechanism. The negligible entropy of activation ($\Delta S^{\ddagger}$ = –3.5 cal K^{-1} mol^{-1})[7,14] possibly arises from the

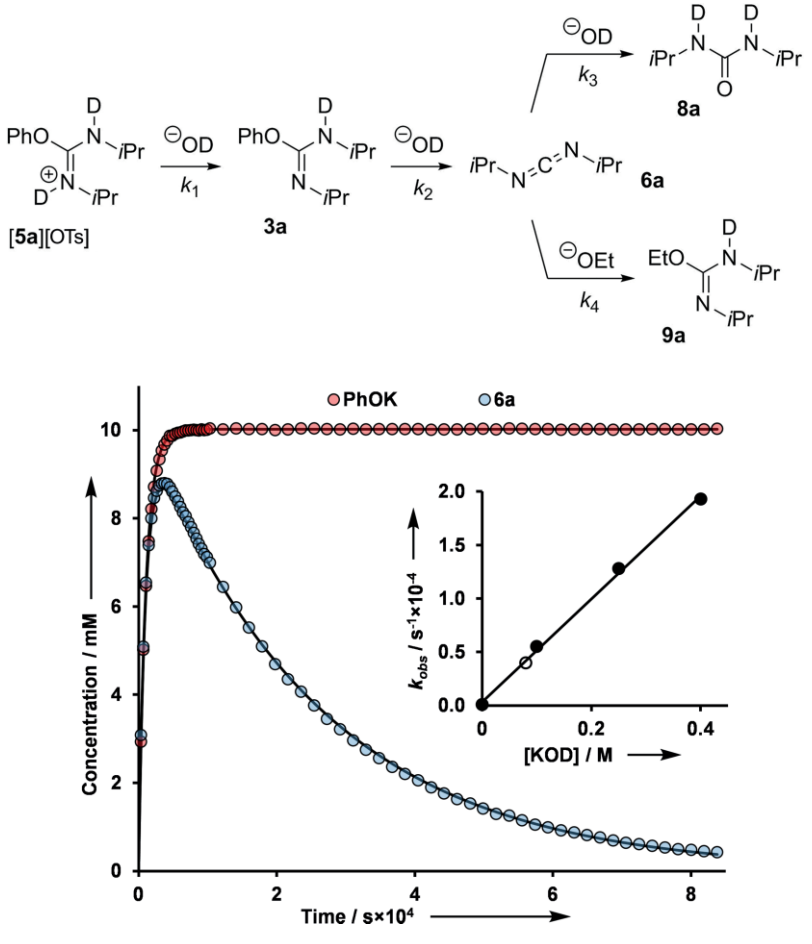


Figure 3. In situ analysis of the reaction of **3a**, liberated in situ (k_1) from [**5a**][OTs], with KOD in 30 % [D_6]EtOD/D_2O, 25 °C, by ^{1}H NMR spectroscopy. Data: circles. Model: solid lines. $k_1 = 1 \times 10^3$ M^{-1} s^{-1} (nominal lower threshold); $k_2 = 1.13 \times 10^{-2}$ M^{-1} s^{-1}; ($k_3 + k_4$) = 4.95×10^{-4} M^{-1} s^{-1}; k_3/k_4 = 13; EtO is C_2D_5O. Inset shows analysis of KOD-catalysed solvolysis of pure diisopropylcarbodiimide **6a** (0.01 M) in 30 % [D_6]EtOD/D_2O (filled circles; $k_{OR} = 4.81 \times 10^{-4}$ M^{-1} s^{-1}), and comparison with the value employed in the model (open circles; $k_3 + k_4$) for solvolysis of in situ liberated **6a**.

phenolate expulsion (+ΔS) being compensated by increasing rigidity in the nascent carbodiimide (–ΔS), although accompanying changes in anion solvation will also contribute.

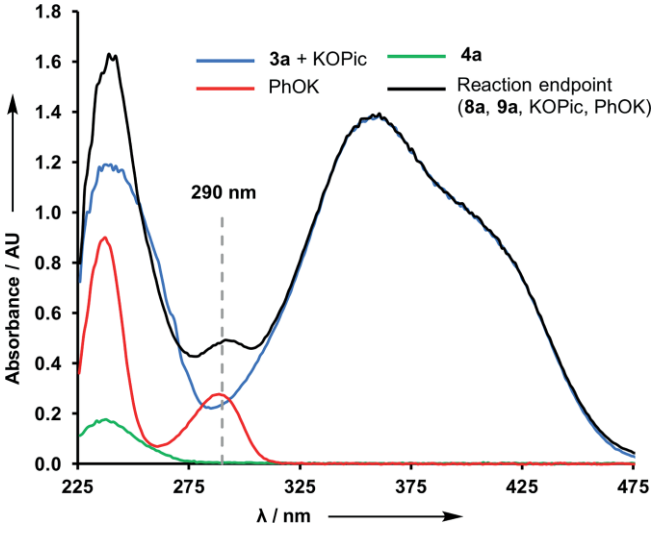


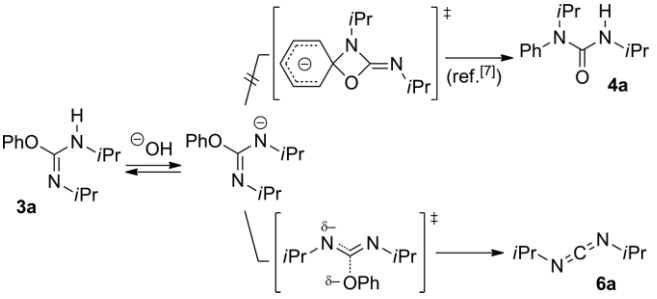
Figure 4. Comparison of reference UV spectra (10^{-4} M in 0.1 M KOH, 0.9 M KCl, 30 % EtOH/H_2O, 25 °C) with the endpoint of reaction of [**5a**][OPic] (10^{-4} M) with 0.1 M KOH (Table 1, Entry 1). During the reaction, the concentration of picrate anion (the strongest UV-absorbing component) is constant. Urea **4a** has a very weak UV signal at 290 nm. Reference [isourea **3a** + KOPic] liberated in situ from [**5a**][OPic].

Conclusions

We have re-investigated a process reported by Suttle and Williams for the preparation and rearrangement of *O*-arylisourea picrate salts [**5**][OPic] to *N*-arylureas **4** (Scheme 3).[7] The generation of *O*-phenylisourea **3a** from PhOH and diisopropylcarbodiimide (**6a**) proceeds as reported, albeit by overall termolecular kinetics that suffer from strong product inhibition through salt formation ([**5a**][OPh]). However, in our hands, the reaction of [**5a**][OPic] (10^{-5} to 10^{-3} M) with excess KOH in 30 % EtOH/H_2O results solely in carbodiimide elimination, not rearrangement. It is salient that *N*-phenylurea **4a** was reportedly identified in situ by UV/HPLC, but not isolated, and that all other *N*-arylureas **4** were assumed to be generated analogously.[7] The k_{OH} value for the reported rearrangement[7] (Table 1, Entry 3) is identical, within experimental error, to that for elimination. Moreover, as **4a** has a very weak UV signal at 290 nm (Figure 4), the only species present that can induce a significant change in absorption (*A*) at the wavelength employed for the determination of k_{OH}[7] is PhOK.

The process monitored (UV; λ = 290 nm) by Suttle and Williams cannot therefore be the rearrangement, and it appears that the kinetics of carbodiimide elimination were misinterpreted[15] as those corresponding to rearrangement[7] (Scheme 5).

In light of this, it is unsurprising that the second-order rates (of solvolysis) were found to correlate with the pK_{aH} of the leaving group (ArOH).[7] The extraordinarily large Brønsted coefficient (β_L = –2.3)[7] is now readily interpreted as arising from rate-limiting phenolate elimination, in an E1cb mechanism. In



Scheme 5. Top: reported[7] hydroxide-catalysed Chapman rearrangement of *O*-phenylisourea **3a**, liberated in situ from [**5a**][OPic] in 30 % EtOH/H_2O. Bottom: revised mechanism in which PhOK elimination generates diisopropylcarbodiimide **6a**, precluding Chapman rearrangement.

summary, in basic aqueous ethanol, the rate of solvolysis of *O*-phenylisourea **3a** precludes what would be a synthetically useful Chapman rearrangement to **4a**. However, it is of note that cyclic *N*-arylguanidines do undergo an analogous anionic Chapman-type rearrangement on deprotonation with KO*t*Bu in DMSO.[8b] Presumably, elimination of a strained cyclic carbodiimide is strongly disfavoured;[16] however, our attempts to induce anionic rearrangement of cyclic *O*-arylisoureas have so far been unsuccessful.

Experimental Section

CAUTION! Picric acid and its salts are not only toxic, but also thermally and shock-sensitive, particularly when dry. These compounds should be used with great caution, on as small a scale as feasible, and with the appropriate level of physical and chemical protection in place.

Preparation of Isourea Salts [5a][OTs] and [5a][OPic]: Phenol (0.47 g, 5 mmol) and diisopropylcarbodiimide (**6a**; 2.32 mL, 15 mmol) were heated at 100 °C under N_2 with stirring for 16 h. Once cooled, the reaction mixture was diluted with CH_2Cl_2 (5 mL) and loaded onto a short column of silica gel. CH_2Cl_2 was passed through the column until the elution of phenol had halted (as determined by TLC, ca. 400 mL of CH_2Cl_2). Et_2O (ca. 100 mL) was used to flush the remaining material off the column, and the eluate was concentrated in vacuo. The residue was dissolved in petroleum ether (b.p. 40–60 °C; 20 mL) and filtered. The filtrate was concentrated in vacuo to yield crude isourea (**3a**; 0.71 g, 3.2 mmol), which was dissolved in CH_2Cl_2 (20 mL) and *p*-toluenesulfonic acid (monohydrate; 0.61 g, 3.2 mmol) added portionwise with rapid stirring over 5 min. After 1 h, the mixture was diluted with CH_2Cl_2 (10 mL) and washed with water (3 × 20 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated in vacuo. Trituration of the resulting oil with Et_2O (10 mL) caused it to solidify. The solid was collected by Büchner filtration, washed with Et_2O (3 × 10 mL) and air-dried. Recrystallisation from *tert*-butyl methyl ether afforded [**5a**][OTs] (0.52 g, 1.3 mmol, 26 %) as colourless needles. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.30 (br. s, 2 H), 7.83 (app d, J_{HH} = 8.2 Hz, 2 H), 7.46 (m, 2 H), 7.28 (m, 1 H), 7.20 (app d, J_{HH} = 8.2 Hz, 2 H), 7.09 (m, 2 H), 3.68 (br. m, 2 H), 2.37 (s, 3 H), 1.20 (d, $^3J_{HH}$ = 6.6 Hz, 12 H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 156.9, 153.2, 142.3, 140.1, 130.9, 128.9, 126.12, 126.07, 115.8, 46.3, 22.6, 21.5 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3177 (w, NH), 2979 (w), 2872 (w), 1668 (m, C=N), 1572 (m), 1487 (m), 1382 (m), 1219 (m), 1177 (m), 1123 (m), 1035 (m), 1012 (m), 815 (m), 754 (m), 679 (s), 561 (m) cm^{-1}. HRMS (EI^+): calcd. for

$C_{13}H_{21}N_2O$ [M]$^+$ 221.16484, found 221.16450. M.p. 91–92 °C. [**5a**][OPic] was prepared by dropwise addition of a solution of crude isourea **3a** (0.76 g, 3.5 mmol), obtained as described above, in 2-propanol (5 mL) to a solution of picric acid (0.8 g, 3.5 mmol) in 2-propanol (75 mL) with rapid stirring over a period of 5 min. A yellow precipitate formed throughout the addition. The suspension was stirred for a further 30 min, then the yellow solid was isolated by Büchner filtration, washed with 2-propanol (3 × 10 mL) to ensure all picric acid was removed, and then air-dried. [**5a**][OPic] (0.99 g, 2.2 mmol, 44 %) was obtained as a bright yellow powder. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.98 (br. s, 2 H), 8.58 (s, 2 H), 7.53 (app t, J_{HH} = 7.6 Hz, 2 H), 7.36 (app t, J_{HH} = 7.6 Hz, 1 H), 7.29 (app d, J_{HH} = 7.6 Hz, 2 H), 3.96 (br. s, 2 H), 1.20 (br. s, 12 H) ppm. ^{13}C{^{1}H} NMR (126 Hz, [D$_6$]DMSO): δ = 160.8, 155.4, 151.8, 141.8, 130.54, 126.4, 125.1, 124.1, 118.7, 45.4 (br. app d), 21.7 (br. app d) ppm. IR (neat): $\tilde{\nu}_{max}$ = 3196 (w, NH), 3063 (w), 2978 (w), 1677 (m, C=N), 1633 (m), 1535 (m), 1463 (m), 1317 (m), 1271 (m), 1192 (m), 1164 (m), 1129 (m), 1077 (w), 926 (w), 912 (w), 804 (w), 742 (m), 709 (w), 685 (w) cm^{-1}. HRMS (EI$^+$): calcd. for $C_{13}H_{21}N_2O$ [M]$^+$ 221.16484, found 221.16435.

Reaction of Isourea Salts with KOH: [**5a**][OPic] (22.5 mg, 0.05 mmol) in EtOH (6 mL) was added with rapid stirring to a solution of KOH (28.1 mg or 281 mg, 0.5 or 5 mmol) in water (35 mL) and EtOH (9 mL). After 44 h, the reaction mixture was extracted with EtOAc (2 × 25 mL). To the organic phase was added [D$_6$]DMSO (1 mL) and the mixture then carefully concentrated by passing a stream of air over the solution whilst it was rapidly stirred. The resulting solution was analysed by ^{1}H NMR spectroscopy (400 MHz) without further purification. Phenol, picric acid, *N*,*N*′-diisopropylisourea (**8a**) and *O*-ethyl-*N*,*N*′-diisopropylisourea (**9a**) were the only species detected. *N*,*N*′-diisopropyl-*N*-phenylisourea (**4a**) could not be detected (<1 %, by reference to ^{13}C satellites of the ^{1}H signals of the phenol). Samples of **4a**, **8a** and **9a**, prepared as outlined below, were used to reference the ^{1}H NMR ([D$_6$]DMSO) spectra.

***N*,*N*′-Diisopropyl-*N*-phenylisourea (4a):**[7] Isopropyl isocyanate (0.20 mL, 2 mmol) was diluted with Et$_2$O (2 mL) under N$_2$. *N*-Isopropylaniline (0.29 mL, 2 mmol) was then added dropwise with stirring over 2 min. After 30 min, the reaction mixture was diluted with EtOAc (10 mL) and washed with HCl (10 % aqueous; 10 mL) and water (2 × 10 mL). The organic layer was dried (MgSO$_4$), filtered and concentrated in vacuo. The resulting crude solid was recrystallised from petroleum ether (b.p. 60–80 °C) to afford **4a** (127 mg, 0.58 mmol, 29 %) as colourless needles. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.45–7.36 (m, 3 H), 7.16–7.13 (m, 2 H), 4.88 (sept, $^3J_{HH}$ = 6.8 Hz, 1 H), 3.93 (sept, $^3J_{HH}$ = 6.5 Hz, 1 H), 3.62 (br. s, 1 H), 1.04 (d, $^3J_{HH}$ = 6.8 Hz, 6 H), 0.99 (d, $^3J_{HH}$ = 6.5 Hz, 6 H) ppm. ^{13}C{^{1}H} NMR (101 Hz, CDCl$_3$): δ = 156.5, 138.2, 131.4, 129.6, 128.3, 46.3, 42.4, 23.5, 21.8 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3438 (w, NH), 2964 (w), 2930 (w), 2876 (w), 1647 (m, C=O), 1489 (m), 1466 (m), 1452 (m), 1321 (m), 1267 (m), 1254 (m), 1170 (m), 1116 (m), 760 (m), 709 (m), 585 (m) cm^{-1}. HRMS (EI$^+$): calcd. for $C_{13}H_{20}N_2O$ [M]$^+$ 220.15701, found 220.15596. M.p. 66–67 °C.

***N*,*N*′-Diisopropylisourea (8a):**[17] Glacial acetic acid (150 µL, 2.6 mmol) was added dropwise over 2 min, with rapid stirring, to a solution of diisopropylcarbodiimide (**6a**; 155 µL, 1 mmol) in petroleum ether (b.p. 40–60 °C; 4 mL). A colourless precipitate formed throughout the addition. After 1 h, the solid was isolated by Büchner filtration, washed with petroleum ether (b.p. 40–60 °C; 3 × 5 mL) and air-dried. Recrystallisation from EtOH afforded **9a** (100 mg, 0.69 mmol, 69 %) as colourless needles. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 5.47 (d, $^3J_{HH}$ = 7.6 Hz, 2 H), 3.63 (dsept, $^3J_{HH}$ = 7.6 and 6.5 Hz, 2 H), 1.00 (d, $^3J_{HH}$ = 6.5 Hz, 12 H) ppm. ^{13}C{^{1}H} NMR (101 Hz, [D$_6$]DMSO): δ = 156.8, 40.7, 23.3 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3341 (w, NH), 2967 (w), 2873 (w), 1616 (m, C=O), 1556 (m), 1464 (w), 1384 (w), 1360 (w), 1325 (w), 1244 (m), 1166 (m), 1129 (m), 628 (m) cm^{-1}. MS (EI$^+$): calcd. for $C_7H_{16}N_2O$ [M]$^+$ 144.13, found 144.1.

***O*-Ethyl-*N*,*N*′-diisopropylisourea (9a):**[18] Diisopropylcarbodiimide (**6a**; 155 µL, 1 mmol) was added with stirring to a suspension of copper(I) chloride (5 mg, 0.05 mmol) in EtOH (1 mL). After 21 h, the mixture was diluted with brine (10 mL) and extracted with Et$_2$O (3 × 10 mL). The combined organic fractions were dried (MgSO$_4$), filtered and carefully concentrated in vacuo (750 mbar, 40 °C; note: product volatile) to approx. 5 mL. The remaining solvent was removed by passing a stream of nitrogen over the solution. The title compound **17** (26 mg, 0.15 mmol, 15 %) was obtained as a pale yellow oil that darkened to a pale green/blue colour over time, indicative of minor quantities of copper-based contaminants. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 4.84 (br. s, 1 H), 3.93 (q, $^3J_{HH}$ = 7.0 Hz, 2 H), 3.64 (br. m, 1 H), 3.34 (br. m, 1 H), 1.13 (t, $^3J_{HH}$ = 7.0 Hz, 3 H), 1.04 (br. d, $^3J_{HH}$ = 6.4 Hz, 6 H), 0.95 (br. d, $^3J_{HH}$ = 6.1 Hz, 6 H) ppm. ^{13}C{^{1}H} NMR (101 Hz, [D$_6$]DMSO): δ = 150.4, 59.5, 44.4 (br), 42.7 (br), 24.7 (br), 23.4 (br), 14.5 ppm. IR (neat): $\tilde{\nu}_{max}$ = 2964 (m, NH), 2931 (w), 2871 (w), 1659 (s, C=N), 1464 (w), 1448 (w), 1366 (m), 1311 (s), 1169 (m), 1123 (w), 1085 (m), 1026 (w), 711 (w), 609 (w), 577 (w), 494 (w) cm^{-1}. HRMS (EI$^+$): calcd. for $C_9H_{20}N_2O$ [M]$^+$ 172.15701, found 172.15763.

Isourea Synthesis Kinetics by ^{1}H NMR Spectroscopy: Figure 1. Phenol (94.1 mg, 1 mmol) was dissolved in CDCl$_3$ (4 mL) under N$_2$; **6a** (150 µL, 0.97 mmol) was added (t = 0) and the resulting mixture very briefly stirred. An aliquot of this solution (0.6 mL) was then transferred to each of four J. Young valve NMR tubes (Samples A, B, C, D). The tube for sample D also contained copper(I) chloride (3.0 mg, 0.03 mmol). The ^{1}H NMR spectra (400 MHz) of these samples were repeatedly recorded between t = 20 min to t = 520 h. At t = 288 h, to sample B was added additional **6a** (23 µL, 0.15 mmol), and to sample C was added additional phenol (14.1 mg, 0.15 mmol). Values for [**6a**]$_t$ were extracted from ^{1}H NMR spectra using MestReNova. DynoChem was used to fit the mechanistic model described in Figure 1 to this data by allowing freedom in k_1, k_{-1} and k_{-2}. The value of k_2 was arbitrarily fixed at 1×10^3 M^{-1} s^{-1}. NMR spectroscopic data for *N*,*N*′-diisopropyl-*O*-phenylisourea (**3a**): ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.31 (app t, J_{HH} = 7.5 Hz, 2 H), 7.07 (app t, J_{HH} = 7.5 Hz, 1 H), 7.01 (app d, J_{HH} = 7.5 Hz, 2 H), 3.74 (sept, $^3J_{HH}$ = 6.4 Hz, 2 H), 1.11 (d, $^3J_{HH}$ = 6.4 Hz, 12 H) ppm.

Solvolysis Kinetics by UV Spectroscopy: Table 1. Stock solutions were prepared using volumetric glassware, and a single stock solution of a given concentration of reagent was used throughout. Dilute stock solutions of isourea salts (0.2 and 0.02 mM) were prepared by sequential dilution. Volumes of stock solutions were measured using Gilson pipettes. Background spectra were recorded after combining a stock solution of EtOH/water (6:4; 1 mL) with an aqueous KOH/KCl stock solution (1 mL) of the appropriate concentration. Background spectra were subsequently subtracted from the UV/Vis absorption spectra of analytes in solutions of the same composition. Reference UV/Vis absorption spectra were recorded immediately after combining stock solutions of the reference compounds (2×10^{-7} mol) in EtOH/water (6:4; 0.2 mM stock; 1 mL) with aqueous KOH/KCl (0.2/1.8 M stock, 0.2 mmol/1.8 mmol; 1 mL). The stock solution of **6a** in EtOH/water (6:4) was used immediately after preparation. The following procedure for kinetic analysis is typical: Stock solutions were pre-heated to 25 °C. Aqueous KOH/KCl (0.2/1.8 M stock, 0.2 mmol/1.8 mmol; 1 mL) was added to [**5a**][OPic] (2×10^{-8} mol) in EtOH/water (6:4; 0.02 mM stock solution; 1 mL) in a cuvette (1 cm pathlength). The cuvette was sealed with a stopper and

briefly shaken before being placed in a thermostatted cell holder. The UV/Vis spectrum of the solution was recorded at 20 s time intervals for 10000 s with an Ocean Optics USB4000 detector and data processed (Kinetic Studio; TgK Scientific) to afford the temporal absorbance (*A*) at 290 nm. The Microsoft Excel Solver Add-in was used to fit d(*A*)/d*t* = *k*[**3a**][KOH] (where *A* = absorbance), by assuming [KOH] = 0.1 M remains constant and solving *k*: $A = -B \times e^{(-k)} + C$ (where *B* and *C* are arbitrary fitting variables).

Solvolysis Kinetics by ^{1}H NMR Spectroscopy: Figure 3. Stock solutions were prepared immediately prior to performing kinetic reactions and were only used once. A pellet of KOH was weighed under N_2, and then the appropriate volume of D_2O added to afford a stock solution of the desired concentration. The following procedure is typical: A sample of [**5a**][OTs] (6.0×10^{-3} mmol, 2.36 mg) was dissolved in [D_6]EtOH (0.18 mL) and added to a 5 mm NMR tube. KOH (0.06 mmol) in D_2O (0.143 M stock; 0.42 mL) was then added (*t* = 0) and the solution briefly shaken. The NMR tube was loaded into the NMR spectrometer (probe temperature 25 °C), and ^{1}H NMR spectra (400 MHz) were recorded at regular time intervals. Values for the concentrations of phenolate and **6a** with respect to time were extracted from the ^{1}H NMR spectra using MestReNova. DynoChem was used to fit the kinetic model in Figure 3, allowing freedom in k_2 and $k_{(3+4)}$. The rate of hydrolysis of **6a** (inset in Figure 3) was measured using the same procedure, but using *N*-phenylurea (1.17 mg, 8.6×10^{-6} mol) as internal standard, and **6a** (0.89 µL, 5.7×10^{-3} mmol; calculated relative to **4a** by ^{1}H NMR integral analysis) dissolved in [D_6]EtOH (0.18 mL) and adding KOH (0.058 mmol, 0.15 mmol and 0.232 mmol, in three separate experiments) in D_2O (0.42 mL stock). The Microsoft Excel Solver Add-in was used to fit the following rate equation to this data: –d[**6a**]/d*t* = *k*[**6a**][KOH], by assuming [KOH] remains constant and solving the following equation for *k*: [**6a**] = $[\mathbf{6a}]_0 \times e^{-kt} + C$ (where *C* is an arbitrary fitting variable).

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Keywords: Ureas · Rearrangement · Elimination · Solvolysis · Reaction mechanisms

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[9] ***CAUTION!*** Picric acid is toxic and thermally and shock-sensitive, particularly when dry.

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[15] One explanation for this outcome is that reference samples of PhOH and **4a**, prepared for product analysis by UV and HPLC, may have become inadvertently mislabelled or interchanged, leading to the conclusion that "90.1 % of the original substrate had been converted into the urea (*NN*'-diisopropyl-*N*'-phenylurea) and that a small proportion (2.7 %) was phenol".

[16] Under these conditions [**5a**][OTs] and **3a** still give carbodiimide **6a**.

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