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**PAPER**

# Solventless selective phosgene-free *N*-carbonylation of *N*-heteroaromatics (pyrrole, indole, carbazole) under mild conditions

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*N*-Heteroaromatics HetNH, such as pyrrole (**1**), indole (**2**) and carbazole (**3**), have been selectively *N*-carbonylated by a direct reaction with diphenyl carbonate (DPC), used as an environmental friendly carbonyl active species in place of toxic and hazardous phosgene. The carbonylation reaction can be effectively catalyzed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), which can act as a base catalyst by activating the HetNH substrate, and as a nucleophile catalyst by activating the organic carbonate. The influence of reaction parameters (temperature, reaction time, DBU load, DPC/HetNH molar ratio) on the productivity of the process has been also investigated. The synthetic methodology does not require severe temperature conditions, is solventless, simple (only one step), efficient and selective, and offers a new solution to the synthesis of synthetically versatile $HetNCO_2Ph$ derivatives through a route alternative to the current traditional phosgenation methods.

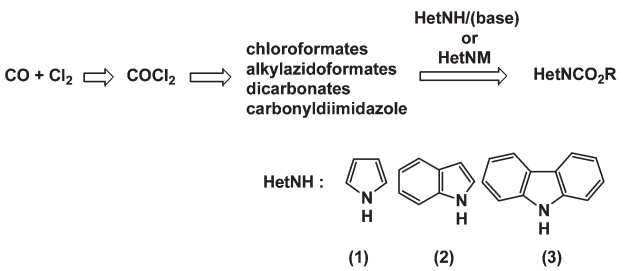
## Introduction

Organic carbonates $(RO)_2CO$ (R = alkyl, aryl), nowadays available through phosgeneless routes even on an industrial scale,[1] are arousing greater and greater interest as environmentally friendly carbonylating agents.[2] So far, a lot of studies have explored the synthetic potential of these compounds in carbonylation reactions of amines for the synthesis of carbamates, isocyanates, ureas.[2,3] Much less, however, is known about their utilization in carbonylation reactions of *N*-heteroaromatic compounds HetNH, such as pyrrole (**1**), indole (**2**), and carbazole (**3**), to $HetNCO_2R$ (R = alkyl, aryl) derivatives (eqn (1)).[4–6]

$$HetNH + (RO)_2CO \rightarrow HetNCO_2R + ROH \qquad (1)$$

$HetNCO_2R$ carbamates are important synthetic intermediates for the preparation of a variety of chemicals, because of widespread use of "$CO_2R$" (R = alkyl, aryl) functionality as a protective group of the N-atom of HetNH substrates.[7] Pyrrole-carbamates are useful starting materials for *C*-functionalisation of the pyrrole ring and the synthesis of pharmaceutically relevant substances or biologically active compounds.[8,9] Carbonyl indole derivatives $HetNCO_2R$ (R = alkyl, aryl) have been utilized as precursors of bromoindole alkaloids[10] and as reagents for the synthesis of more complex heterocyclic systems.[11,12] Under suitable conditions, *N*-phenoxocarbonyl derivatives $HetNCO_2Ph$ (HetNH = pyrrole, indole, carbazole) can act as carbonylating agents and be converted into unsymmetrical ureas $HetNC(O)NR_2$[3a] or undergo transesterification with alcohols to $HetNCO_2R$ compounds,[5] which are useful precursors of the corresponding *N*-alkyl derivatives HetNR (R = alkyl).[4c,d,6a,13]

The methods of synthesis of heterocarbamates $HetNCO_2R$ (R = alkyl, aryl) are still based on harmful and risky phosgene,[14] whose use in the chemical industry meets, nowadays, growing restrictions due to governmental policies for environmental protection, and, in fact, imply the use of phosgene-derivatives like dicarbonates,[9a,15] alkyl-azidoformates,[16] 1,1′-carbonyldiimidazole,[17] chloroformates[18] as sources of the carbonyl moiety (Scheme 1). In most cases the preliminary conversion of HetNH into a more nucleophilic HetNM (M = alkali metal) salt is required.[16,18a–c,e,f] A relatively more recent protocol (Scheme 2)[19a,b] is based on the activation of carbamic acid $HetNCO_2H$ (HetNH = pyrrole, indole) to $(HetNC(O))_2O$ anhydride. However, this method, which requires a stoichiometric amount of the phosgene-derivative EDCI·HCl ([(3-dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride)[19c] for the activation step, is atomically uneconomical as it involves a multistep procedure and needs two moles of HetNH (for preforming the anhydride) *per* mol of product.




**Scheme 1** Conventional phosgene-based synthetic routes to $HetNCO_2R$ carbamates.

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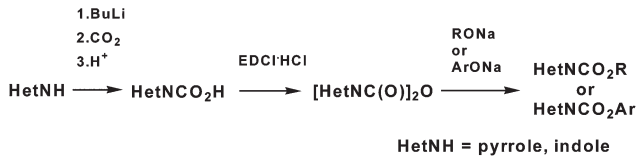
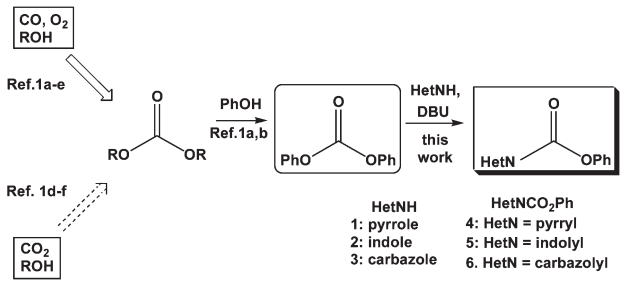



**Scheme 2** Synthesis of $HetNCO_2R$ carbamates *via* $HetNCO_2H$ activation.




**Scheme 3** Phosgeneless route to heterocarbamates $HetNCO_2Ph$.

The reaction of HetNH substrates with carbonic acid diesters (eqn (1)) may provide a potential direct route to the synthesis of *N*-carbonyl derivatives $HetNCO_2R$ (R = alkyl, aryl) and offer an intriguing alternative to the classic phosgenation methods. A few pioneering studies described the synthesis of heteroaromatic carbamates $HetNCO_2R$ (HetNH = pyrrole, indole; R = alkyl) by the reaction of preformed pyrryl or indolyl HetNM salts (M = K, Na, Li, MgBr) with $(MeO)_2CO$[20a] or $(EtO)_2CO$[18a,20a] or $^t$BuOC(O)OPh.[20b] Only recently a few studies[4–6] have reported on the direct *N*-alkoxycarbonylation of *N*-heteroaromatics as pyrrole or carbazole or indoles with dialkyl carbonates (dimethyl carbonate (DMC),[4a–c,e,5,6] dibenzyl carbonate[4d,5]) or alkyl aryl carbonates (methyl phenyl carbonate,[5] *t*-butyl phenyl carbonate[5]) with variable selectivity depending on the catalyst used (tetrabutylammonium bromide,[4b] 4-dimethylaminopyridine,[4c] 1,4-diazabicyclo-[2.2.2]octane,[4a,c,d] amidine[4c,d,5,6a] or phosphazene[5,6a] superbases, solid bases (CaO),[6b] ionic liquids[6c]) and the working conditions.

To date, the direct reaction of diaryl carbonates with HetNH substrates has received very poor attention. In this paper, as part of our efforts devoted to developing a phosgene-free chemistry based on safe non-toxic carbonyl active species which can serve as phosgene substitutes,[2,3a,f–h,5,6a] we focus on industrially relevant diphenyl carbonate (DPC)[1a,b] and explore its potential as a carbonylating agent of pyrrole (**1**), indole (**2**) and carbazole (**3**) in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the catalyst of the carbonylation process (Scheme 3). A few very preliminary results of this research have been described in a short account elsewhere.[5] Herein, we report a detailed study of the carbonylation reaction (eqn (1), R = Ph) and shed light on the possible mechanistic pathways by probing the role played by the amidine catalyst in the process.

## Results and discussion

### Carbonylation of pyrrole, indole, and carbazole with diphenyl carbonate: catalytic activity of DBU

In this study we avoided drastic working temperatures (generally, ≤393 K) and only for the case of pyrrole we explored relatively more severe temperature conditions (433 K). Moreover, we excluded the use of any organic solvent as the reaction medium, and used low-melting DPC (mp: 353 K), which was reacted in excess with respect to HetNH, as the reactant and solvent. Generally, under the working catalytic conditions, a homogeneous reacting system was obtained within variable times, depending on reaction temperature, loading of DBU, DPC/HetNH molar ratio, and the nature of the investigated substrate (**1**, mp: 250 K; **2**, mp: 326 K; **3**, mp: 520 K).

In the absence of any catalyst, substrates **1–3** exhibited very poor reactivity towards DPC (Table 1). Addition of DBU to the reaction mixture modified the reactivity of the system and promoted the selective formation of $HetNCO_2Ph$ derivatives **4–6** (eqn (1), R = Ph) with yields which depended on the working conditions.

**Influence of reaction parameters.** At a temperature as mild as 343 K, using a DPC/HetNH molar ratio close to 4, pyrrole, indole and carbazole were respectively carbonylated to **4**, **5** and **6** in the presence of sub-stoichiometric amounts of DBU (entries 1–3, Table 2). The TON ($mol_{HetNCO_2Ph}/mol_{DBU}$) values higher than unity (entry 1: TON ≈ 6; entry 2: TON ≈ 50; entry 3: TON ≈ 9) established unambiguously that DBU acts as a catalyst for the carbonylation process. In experiments 1–3 (Table 2) a homogeneous reaction mixture was obtained at the working temperature (343 K), differently from what was observed, at 333 K,

**Table 1** Reactivity of HetNH (**1–3**) towards DPC in the absence of any catalyst[a]

| Entry | HetNH (mmol) | DPC/HetNH (mol/mol) | *T*/K | *t*/h | $HetNCO_2Ph$ GC-yield [%] |
|---|---|---|---|---|---|
| 1 | **1**(3.60) | 3.89 | 343 | 9 | — |
| 2 | **1**(3.60) | 3.89 | 393 | 12 | — |
| 3 | **2**(1.20) | 3.97 | 343 | 24 | — |
| 4 | **2**(1.25) | 3.82 | 393 | 15 | 5[b] |
| 5 | **3**(1.21) | 3.90 | 393 | 15 | 2[b] |

[a] Under the working conditions a homogeneous system was rapidly obtained, except for entry 5. In the latter case, the reaction mixture remained heterogeneous throughout the reaction time because of non-complete solubilization of solid **3** in melted DPC at the working temperature (393 K). [b] The GC analysis of the reaction mixture did not show any significant presence of other products besides minor amounts of $HetNCO_2Ph$ and phenol.

**Table 2** Carbonylation of HetNH (**1–3**) to $HetNCO_2Ph$ (**4–6**) with DPC in the presence of DBU at different temperatures[a]

| Entry | HetNH (mmol) | DPC/HetNH (mol/mol) | DBU[b] (mol%) | *T*/K | *t*/h | GC-yield[c] [%] |
|---|---|---|---|---|---|---|
| 1 | **1**(3.60) | 3.89 | 9.3 | 343 | 24 | 62 |
| 2 | **2**(1.20) | 3.96 | 1.1 | 343 | 24 | 55 |
| 3 | **3**(1.23) | 3.98 | 9.3 | 343 | 22 | 89 |
| 4 | **1**(3.60) | 3.89 | 9.3 | 393 | 1 | 57 |
| 5 | **2**(1.24) | 3.98 | 1.1 | 393 | 6 | 75 |
| 6 | **3**(1.20) | 3.79 | 9.4 | 393 | 0.5 | 87 |

[a] At the working temperature a homogeneous mixture was obtained. [b] *Vs.* HetNH. [c] Of $HetNCO_2Ph$. The GC analysis of the reaction mixture did not show any significant formation of other products besides $HetNCO_2Ph$ and PhOH.

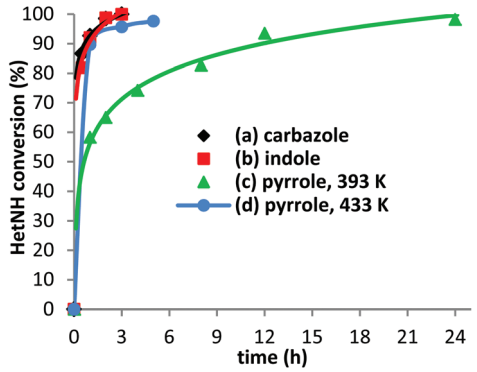



**Fig. 1** Carbonylation of HetNH (**1–3**) with DPC (DPC/HetNH ≈ 4 : 1 mol/mol) in the presence of DBU (≈10 mol% *vs.* HetNH).[21] (a) DPC/**3** = 3.8 ± 0.1 mol/mol; DBU/**3** = 9.3 ± 0.1 mol%; 393 K. (b) DPC/**2** = 3.9 ± 0.1 mol/mol; DBU/**2** = 10.3 ± 0.8 mol%; 393 K. (c) DPC/**1** = 3.9 ± 0.1 mol/mol; DBU/**1** = 9.3 mol%; 393 K. (d) DPC/**1** = 3.9 ± 0.1 mol/mol; DBU/**1** = 9.3 mol%; 433 K.

for an ≈ 4 : 1 : 0.1 (mol/mol) DPC/**3**/DBU mixture. In the latter case, most of DPC and **3** remained in the solid state throughout the reaction time (24 h). This may explain why, at 333 K, the latter system showed poor reactivity. At the higher temperature of 393 K the productivity of the carbonylation reaction was markedly higher and conversions to carbamate interesting from a synthetic point of view were achieved selectively within significantly shorter reaction times (entries 4–6, Table 2).

Curves (a)–(c) in Fig. 1 show the conversion of the different substrates as a function of time, at 393 K, when using a DPC/HetNH/DBU molar ratio close to 4 : 1 : 0.1. The curves indicate that **1** is less reactive than **2** and **3**. Under the working conditions, indole and carbazole reacted selectively (≥99%) and quantitatively (100%) within comparable short times (2–3 h). At 393 K, under otherwise analogous conditions, the quantitative conversion of pyrrole (98%) needed a longer time (24 h), which, however, reduced markedly at the working temperature of 433 K (curve (d), Fig. 1; 98% conversion after 5 h). Remarkably, the use of the higher temperature (433 K) did not produce any diminution of carbamate selectivity, which remained very high (≥99%) even at 433 K.

The carbonylation process was studied, at 393 K, in the presence of lower catalyst loadings. Fig. 2 illustrates the results obtained for the carbonylation of carbazole. At the working temperature (393 K), a catalyst load as low as 1.1 mol% promoted selectively (>99%) the phenoxycarbonylation of **3** in quantitative yield within 25 h. Fig. 3 (curve (b)) shows that, under analogous experimental conditions, also indole was selectively (≥99%) carbonylated satisfactorily (94%, after 25 h), while the conversion of pyrrole to 1-phenoxycarbonyl pyrrole was modest and did not exceed 52% (≈99% selectivity) after 24 h (curve (c)). At 393 K, keeping unchanged the DPC/HetNH molar ratio (≈4), **1**, the least reactive of the substrates investigated, can be carbonylated more effectively by employing higher catalyst loadings (Fig. 4, curves (b) and (c)). In general, the use of higher catalyst loads allowed us to shorten the conversion times and to work very efficiently at lower temperatures. Accordingly, using a stoichiometric amount of DBU (1 equiv.), all the substrates **1–3** were quantitatively and selectively carbonylated

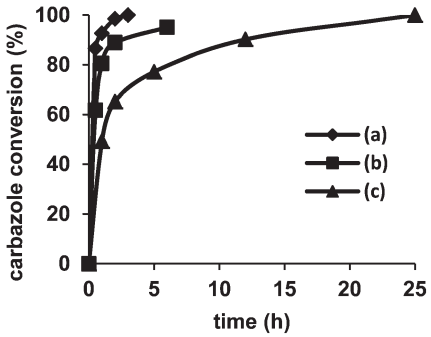



**Fig. 2** Carbonylation of carbazole with DPC (DPC/**3** ≈ 4 : 1 mol/mol) in the presence of DBU, at 393 K: influence of catalyst loading.[21] (a) DPC/**3** = 3.8 ± 0.1 mol/mol; DBU/**3** = 9.3 ± 0.1 mol%. (b) DPC/**3** = 3.9 ± 0.1 mol/mol; DBU/**3** = 3.9 ± 0.1 mol%. (c) DPC/**3** = 3.9 ± 0.1 mol/mol; DBU/**3** = 1.1 ± 0.1 mol%. Selectivity to **6**: ≥99%.

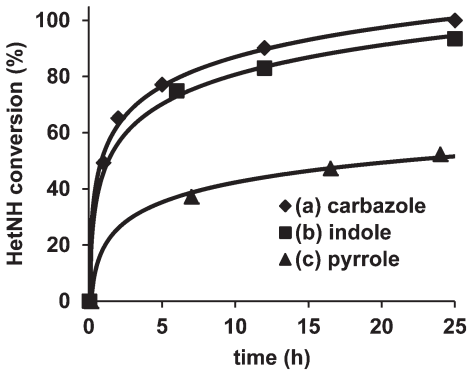



**Fig. 3** Carbonylation of HetNH (**1–3**) with DPC (DPC/HetNH ≈ 4 : 1 mol/mol) in the presence of DBU (≈1 mol% *vs.* HetNH), at 393 K.[21] (a) HetNH: carbazole; DPC/**3** = 3.9 ± 0.1 mol/mol; DBU/**3** = 1.1 ± 0.1 mol%. (b) HetNH: indole; DPC/**2** = 3.9 ± 0.1 mol/mol; DBU/**2** = 1.1 ± 0.1 mol%. (c) HetNH: pyrrole; DPC/**1** = 3.9 ± 0.1 mol/mol; DBU/**1** = 0.93 mol%.

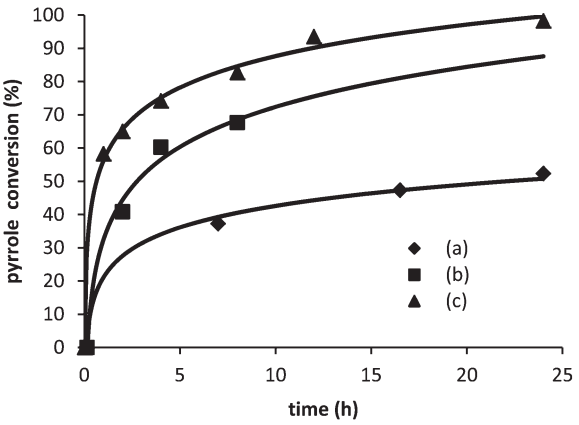



**Fig. 4** Reaction of pyrrole with DPC (DPC/**1** ≈ 4 : 1 mol/mol) in the presence of DBU, at 393 K: influence of catalyst loading.[21] (a) DPC/**1** = 3.9 ± 0.1 mol/mol; DBU/**1** = 0.93 mol%. (b) DPC/**1** = 3.9 ± 0.1 mol/mol; DBU/**1** = 3.5 mol%. (c) DPC/**1** = 3.9 ± 0.1 mol/mol; DBU/**1** = 9.3 mol%.

**Table 3** Carbonylation of HetNH (**1–3**) to $HetNCO_2Ph$ (**4–6**) with DPC in the presence of 1 equiv. of DBU, at 333 K[a,b]

| Entry | HetNH (mmol) | DPC/HetNH (mol/mol) | DBU[c] (mol%) | *t*/h | HetNH conversion [%] |
|---|---|---|---|---|---|
| 1 | **1**(3.60) | 3.92 | 102 | 3 | 97 |
| 2 | **2**(3.69) | 3.81 | 100 | 3 | 100 |
| 3 | **3**(3.59) | 3.91 | 102 | 3 | 100 |

[a] $HetNCO_2Ph$ selectivity was ≥99%. [b] At the working temperature a homogeneous mixture was obtained. [c] *Vs.* HetNH.

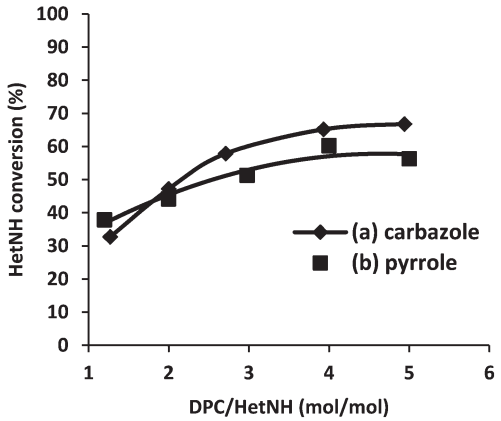



**Fig. 5** Carbonylation of HetNH (**1** or **3**) with DPC in the presence of DBU at 393 K: influence of DPC/HetNH molar ratio.[21] (a) HetNH: carbazole; DBU = 1.1 ± 0.1 mol% *vs.* **3**; reaction time = 2 h. In the range 1.3–2 mol/mol the reaction mixture remained heterogeneous throughout the reaction time (2 h), as **3** did not dissolve completely in the reaction medium (melted DPC). In all the runs selectivity was higher than 99%. (b) HetNH: pyrrole; DBU = 3.53 mol% *vs.* **1**; reaction time = 4 h. In all the runs selectivity was close to 99%.

within very short times (3 h) at the temperature of 333 K (entries 1–3, Table 3).

We have also investigated the influence of the DPC/HetNH molar ratio (Fig. 5). Curve (a) in Fig. 5 shows the change of carbazole conversion against the DPC/HetNH (HetNH = **3**) molar ratio, when the reaction was carried out at 393 K for 2 h with a DBU load close to 1 mol% (*vs.* **3**). Curve (b) in Fig. 5 illustrates the analogous change in the case of less reactive pyrrole (HetNH = **1**), when the latter substrate was reacted with DPC at 393 K for 4 h in the presence of 3.5 mol% of DBU (*vs.* **1**). In both cases, the use of a DPC/HetNH molar ratio higher than 4 did not offer any substantial advantage as it produced only a little variation of substrate conversion to carbamate. Conversely, substrate conversion decreased upon using DPC/HetNH molar ratios lower than 4. The above results justify the DPC/HetNH molar ratios close to 4 used in the present work. The excess of DPC can be recovered in a pure form with high yield, as we have demonstrated for the specific cases of carbonylation of indole and pyrrole.[22]

**Carbamate selectivity.** Formation of $HetNCO_2Ph$ heterocarbamate was very selective. The *N*-carbonylation reaction proceeded regioselectively without any significant incidence of *C*-carbonylation. *C*-Carbonylation products may form in variable yield, depending on the working conditions, when HetNM (Li, Na, K, MgX) salts are allowed to react stoichiometrically with carbonylating agents, such as organic carbonates, chloroformates, or isocyanates.[18a,20a,23]

In principle, the reaction of HetNH with DPC might also result in the side-generation of $(HetN)_2CO$ ureas (eqn (2)) through consecutive processes involving (i) the preliminary formation of

$$2HetNH + (PhO)_2CO \rightarrow (HetN)_2CO + 2PhOH \qquad (2)$$

$HetNCO_2Ph$ (eqn (1), R = Ph) and (ii) the further conversion of the latter species into $(HetN)_2CO$ (eqn (3)).

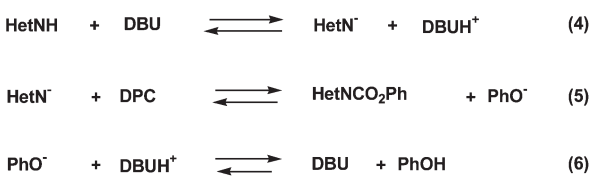
$$HetNCO_2Ph + HetNH \rightarrow (HetN)_2CO + PhOH \qquad (3)$$

Under the above catalytic conditions, $(HetN)_2CO$ species, if any, formed in very minor amounts. However, the formation of ureidic derivatives may become more important, even at ambient temperature, when using a larger amount of HetNH relative to DPC, as has been found for the specific case of pyrrole. For instance, at 293 K, in the presence of DBU, a homogeneous mixture of **1** and DPC (**1**/DBU/DPC = 1 : 1 : 0.5 mol/mol) converted into **4** and 1,1′-carbonyldipyrrole. After 9 h the conversion of **1** was around 50%, and **4** and 1,1′-carbonyldipyrrole formed in an ≈3 : 1 molar ratio. The composition of the reaction mixture did not undergo any appreciable change by prolonging the reaction time for a further 15 h, suggesting that an equilibrium state was likely reached. Accordingly, using a greater excess of **1** led to a significant increase of 1,1′-carbonyldipyrrole yield relative to **4**. For instance, after 24 h at 293 K, **4** and 1,1′-carbonyldipyrrole were obtained in approximately equimolar amounts, when **1**, DBU and DPC were reacted in a 5 : 1 : 0.5 molar ratio. Through this way, which allowed us to bypass the traditional synthetic routes to $(HetN)_2CO$ ureas based on the direct use of phosgene[24] or 1,1′-carbonyldiimidazole (a phosgene-derivative),[25] we succeeded in isolating 1,1′-carbonyldipyrrole with yields close to 50% (*vs.* DPC).

## Role of DBU

The catalytic role played by DBU in the carbonylation process (eqn (1), R = Ph) was probed. We focused on the reactivity of the amidine catalyst not only as a base, but also as a nucleophile.[26]

**HetNH activation: base catalysis.** In principle, by acting as a proton acceptor DBU can activate the substrate and convert HetNH into the more nucleophilic $HetN^-$ anion according to reaction (4) (Scheme 4). The effectiveness of equilibrium (4) has




**Scheme 4** Base catalysis.

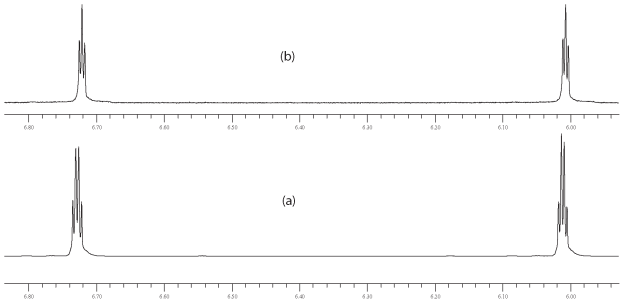


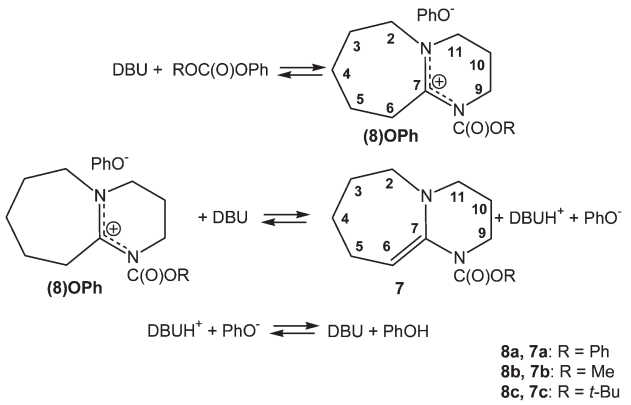

**Fig. 6** $^1$H NMR (500 MHz; $(CD_3)_2SO$ (1 mL); 293 K): (a) pyrrole (15 μL, 0.216 mmol); (b) pyrrole (15 μL, 0.216 mmol)/DBU (35 μL, 0.234 mmol) mixture.

been documented experimentally by $^1$H NMR (500 MHz, $(CD_3)_2SO$, 293 K) spectroscopy for the specific case of pyrrole, the least acidic of the *N*-heteroaromatic substrates considered in this study.[27,28] As a matter of fact, DBU promotes the "exchange decoupling"[29] between the pyrrolic protons $H_\alpha$ and $H_\beta$ and the N–H proton of the heteroaromatic substrate. Accordingly, in the proton spectrum of an equimolar **1**/DBU mixture (Fig. 6, spectrum (b)) the resonances of $H_\alpha$ and $H_\beta$ protons of pyrrole were no longer quartets, but triplets ($J = 2$), as a result of the fact that, in the presence of the base (eqn (4)), the expected coupling of $H_\alpha$ and $H_\beta$ with the N–H proton was washed out. This behaviour is reminiscent of that exhibited by **1** in the presence of piperidine,[30] a weaker base than DBU.

The above findings make plausible the hypothesis that a base catalysis may be operative (Scheme 4). A base catalysis has been proposed by Sun for the *N*-methoxycarbonylation of **1** with DMC over solid base (CaO) catalysts.[6b] In our case, the p$K_a$ values of the HetNH substrates (**1–3**) and $DBUH^+$ suggest that equilibrium (4) lies to the left.[31] Although the $HetN^-$ anion is expected to be present in the reaction medium at low concentration, it may be reactive enough, under the working conditions, as to react with the organic carbonate and to generate the relevant *N*-phenoxycarbonylation product (Scheme 4, eqn (5)). In this regard, it is worth reminding that HetNM (M = Li, Na, K, MgX) salts of pyrrole and indole can react with organic carbonates, such as dimethyl, diethyl, *tert*-butyl phenyl carbonate, to give the corresponding methyl, ethyl, *tert*-butyl carbamates.[18a,20]

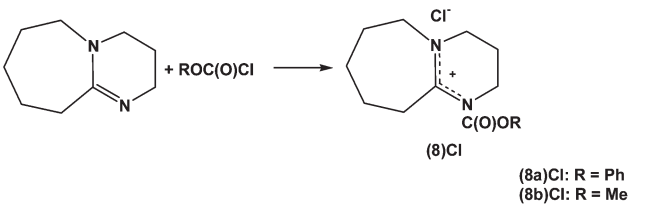
The catalyst (DBU) can be regenerated according to equilibrium (6). The p$K_a$ values of PhOH and $DBUH^+$ in different media ($H_2O$ or DMSO)[27] suggest that the position of equilibrium (6) may depend markedly on the nature of the solvent. In DMSO, a polar aprotic medium (like melted DPC), equilibrium (6) may lie to the right.[27] Moreover, under our catalytic conditions, the location of equilibrium (6) is expected to vary with time as a result of phenol co-production. This may affect the activity of the catalytic system in the long run.

**DPC activation: nucleophilic catalysis.** The ability of DBU to act as a nucleophile towards a variety of electrophiles has been long recognized.[26] In a recent study,[26b] we have demonstrated that organic carbonates, such as DPC itself, can be activated nucleophilically by DBU through the formation of an *N*-alkoxycarbonyl ketene aminal **7** as the ultimate product (Scheme 5). The latter species may form through deprotonation of the

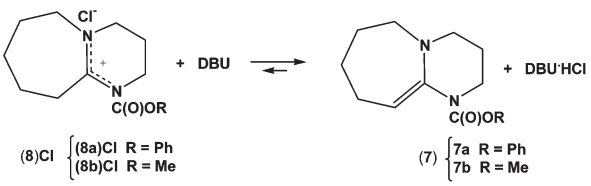



**Scheme 5** Reactivity of DBU with carbonic acid diesters.[26b]

corresponding *N*-alkoxycarbonyl amidinium cations **8** by the amidine base, as we have demonstrated experimentally by isolating and characterizing a few **8** chloride salts, such as (**8a**)Cl and (**8b**)Cl·$H_2O$ (eqn (7)), and studying their reactivity towards the organic base (eqn (8)).[26b] Ketene aminals **7** are more active carbonylating species than amidinium ions **8** and organic carbonates from which they derive (Scheme 5), and can function as "$CO_2R$" carriers, as they can transfer the alkoxycarbonyl group to a nucleophile as methanol, for instance, and regenerate the amidine base.[26b]

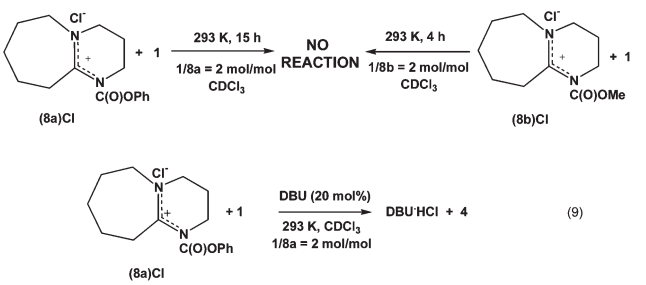



(7)




(8)

The above findings raise the question whether, in the catalytic process here investigated (eqn (1), R = Ph), the formation of heterocarbamates $HetNCO_2Ph$ (**4–6**) may involve DBU-promoted




(9)

**Scheme 6** Reactivity of (**8**)Cl salts with pyrrole in the absence and in the presence of DBU.

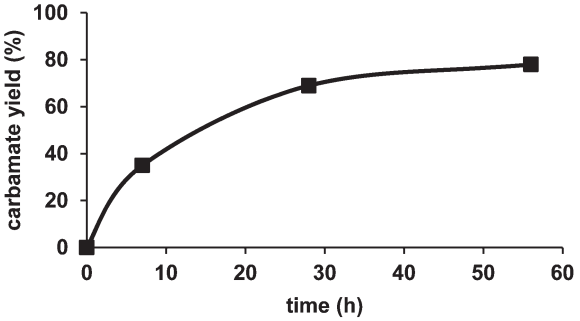
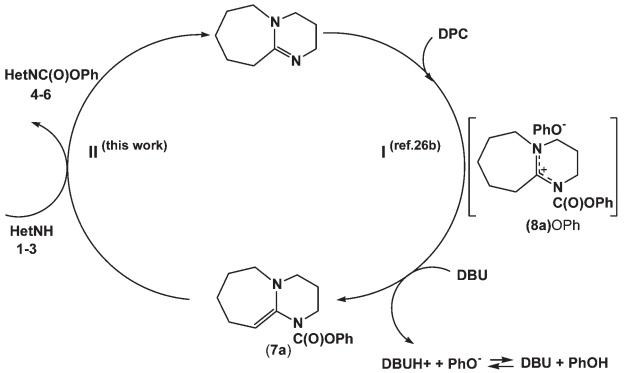



**Fig. 7** Reaction of **7b** with pyrrole (**1**/**7b** = 2 mol/mol), in $CDCl_3$, at 293 K. Yield of 1-methoxycarbonyl pyrrole *versus* time.

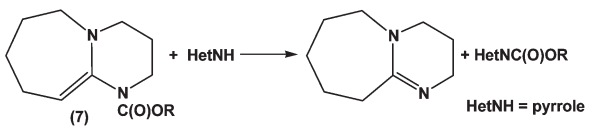



**Scheme 7** Nucleophilic catalysis.

nucleophilic activation of DPC (Scheme 5) as an additional reaction pathway. In tackling this issue, once more we selected pyrrole as the reference substrate and investigated the reactivity of **1** towards *N*-alkoxycarbonyl amidinium salts (**8a**)Cl and (**8b**)$Cl{\cdot}H_2O$ and ketene aminal **7b**.

At ambient temperature, in $CDCl_3$, pyrrole did not react with either (**8a**)Cl or (**8b**)$Cl{\cdot}H_2O$ (Scheme 6). However, addition of DBU altered the reactivity of the system. For instance, at 293 K, in $CDCl_3$ and in the presence of DBU (20 mol% *vs.* the salt), pyrrole reacted with (**8a**)Cl (eqn (9)) to give DBU·HCl and **4**, albeit slowly under the working conditions (≈20% *vs.* **8a**, after 65 h). In principle, the change of reactivity observed upon addition of DBU might be ascribed to the formation of a pyrryl anion (eqn (4)), a more nucleophilic species than pyrrole (see above). However, soon after adding DBU to the $CDCl_3$ solution of (**8a**)Cl and **1**, we noted that the NMR spectrum of the reaction mixture (see Experimental) also showed the presence, in solution, of ketene aminal **7a** (eqn (8)). The resonances of both **7a** and **8a** remained clearly distinguishable in the spectrum throughout the reaction time (65 h).

The latter fact suggested that reaction (9) may proceed through the intermediate formation of **7a** (eqn (8)) and involve, as a subsequent step, the reaction of **7a** with pyrrole (eqn (10), R = Ph). Substantial support for this hypothesis has been obtained by




(10)

reacting pyrrole with ketene aminal **7b**. In fact, at 293 K, in $CDCl_3$, **7b** and pyrrole reacted to afford 1-methoxycarbonyl pyrrole (eqn (10), R = Me) with 78% yield after 56 h (Fig. 7). The formation of $HetNCO_2Me$ (HetNH = pyrrole) was ascertained not only by means of NMR spectroscopy ($^1H$, $^{13}C$), but also by GC/MS (see Experimental).

These results provide further evidence supporting the fact that ketene aminal **7** can behave as a carrier of the $CO_2R$ group.[26b] Moreover, the above findings substantiate the pathway concisely illustrated in Scheme 7 as an additional accessible mechanistic route for the catalytic process under study. Scheme 7 summarizes a nucleophile catalysis, whose key steps, I and II, have been documented experimentally. In step I the organic carbonate is nucleophilically activated by DBU and converted, through the intermediacy of (**8a**)OPh, into ketene aminal **7a**, which, then, transfers the $CO_2Ph$ moiety to HetNH and regenerates the catalyst (step II).[33]

## Conclusions

DPC has been investigated as a carbonylating agent of pyrrole, indole and carbazole. The carbonylation of these substrates with DPC provides a solution to the synthesis of heterocarbamates $HetNCO_2Ph$ (HetNH = pyrrole, indole, carbazole) through a phosgene- and halogen-free synthetic route (Scheme 3), which is safe and avoids the heavy cogeneration of wastes (salts, *etc.*) typical of classic phosgenation protocols. The developed synthetic methodology is solventless, direct (only one step), selective and high yield. The carbonylation reaction can be effectively catalyzed, under usually non severe temperature conditions, by DBU, acting not only as a base, by activating the substrate HetNH to $HetN^-$, but also as a nucleophile towards DPC.

## Experimental

### General methods

All solvents were dried according to conventional methods ($P_2O_5$; Na–benzophenone)[34] and stored under $N_2$. DPC, DBU, **1**, **2** and **3** were commercial products (Fluka, Aldrich, Carlo Erba). Pyrrole was dried over $CaH_2$, filtered, distilled *in vacuo* over fresh $CaH_2$, stored and manipulated under $N_2$. DBU was used as received and manipulated under an inert atmosphere to prevent contamination by atmospheric $CO_2$ or moisture. Ketene aminal **7b** and salts (**8a**)Cl and (**8b**)$Cl{\cdot}H_2O$ were prepared as previously described.[26b] GC analyses were performed with an HP 5890 Series II gas-chromatograph (capillary column: Heliflex AT-5, 30 m × 0.25 mm, 0.25 μm film thickness). GC-MS analyses were carried out with a Shimadzu GC-17A linked to a Shimadzu GC-MS QP5050 selective mass detector (capillary column: Supelco MDN-5S, 30 m × 0.25 mm, 0.25 μm film thickness). IR spectra were taken on a Shimadzu FTIR Prestige 21 spectrophotometer. NMR spectra were run with a Bruker AM 500 spectrometer or with a Varian Inova 400 instrument. Chemical shifts are in $\delta$ (ppm) *vs.* $Me_4Si$. Coupling constants are in Hz.

### Carbonylation of HetNH (1–3) with DPC in the presence of DBU: general procedure

Into a 30 mL Schlenk tube, containing the heteroaromatic substrate HetNH (typically ≈1.2 mmol for **2** and **3**; 1.8 or 3.6 mmol for **1**) and the organic carbonate, the catalyst (DBU) was added. The reaction mixture was heated in an oil bath to the working temperature and allowed to react for a given time (for further details see Tables 2 and 3, and the legends of Fig. 1–5). The mixture was cooled to room temperature, dissolved in diethyl ether and analyzed by GC (internal standard: *n*-dodecane) or GC/MS.

The isolation and spectroscopic characterization of compounds **4–6** as well as 1,1′-carbonyl dipyrrole have been described elsewhere.[5,22]

### HetNH activation: $^1$H and $^{13}$C NMR spectra of the pyrrole/DBU system in $(CD_3)_2SO$

The $^1$H and $^{13}$C NMR spectra of an equimolar mixture of pyrrole (15 μL, 0.216 mmol) and DBU (35 μL, 0.234 mmol) in $(CD_3)_2SO$ (1 mL) were measured and compared with those of DBU (35 μL, 0.234 mmol) and pyrrole (15 μL, 0.216 mmol), in the same solvent (1 mL), under otherwise similar experimental conditions.

**Pyrrole/DBU mixture in $(CD_3)_2SO$.** $\delta_H$ (500 MHz, 293 K) 1.44–159 (6 H, m, 3-H, 4-H, 5-H), 1.64 (2 H, quint, $J$ = 5.9, 10-H), 2.24 (2 H, m, 6-H), 3.07 (2 H, t, $J$ = 5.5, 2-H), 3.13 (4 H, m, 9-H and 11-H), 6.01 (2 H, t, $J$ = 2.0, $H_{\beta,pyrr}$), 6.72 (2 H, t, $J$ = 2.0, $H_{\alpha,pyrr}$), 10.93 (1 H, br s, $NH_{pyrr}$). $\delta_C$ (125 MHz, 293 K) 22.34 (10-C), 25.79 (4-C), 28.10 (3-C), 29.08 (5-C), 36.37 (6-C), 43.48 (9-C), 47.48 (2-C), 51.78 (11-C), 159.66 (7-C), 107.01 ($C_{\beta,pyrr}$), 117.27 ($C_{\alpha,pyrr}$).

**Pyrrole in $(CD_3)_2SO$.** $\delta_H$ (500 MHz, 293 K) 6.01 (2 H, q, $J$ = 2.0, $H_\beta$), 6.73 (2 H, q, $J$ = 2, $H_\alpha$), 10.75 (1 H, br s, NH). $\delta_C$ (125 MHz, 293 K) 107.10 ($C_\beta$), 117.35 ($C_\alpha$).

**DBU in $(CD_3)_2SO$.** $\delta_H$ (500 MHz, 293 K) 1.44–158 (6 H, m, 3-H, 4-H, 5-H), 1.63 (2 H, quint, $J$ = 5.9, 10-H), 2.23 (2 H, m, 6-H), 3.05 (2 H, t, $J$ = 5.7, 2-H), 3.12 (4 H, m, 9-H and 11-H). $\delta_C$ (125 MHz, 293 K): $\delta$ = 22.36 (10-C), 25.80 (4-C), 28.11 (3-C), 29.07 (5-C), 36.40 (6-C), 43.52 (9-C), 47.46 (2-C), 51.76 (11-C), 159.48 (7-C).

### Reaction of (8a)Cl with pyrrole in the presence of DBU

To a solution of (**8a**)Cl (39.7 mg, 0.129 mmol) and **1** (18 μL, 0.259 mmol) in $CDCl_3$ (1 mL), DBU (4 μL, 0.0268 mmol) was added. The reaction solution was analyzed, at 293 K, by $^1$H (400 MHz) and $^{13}$C (100 MHz) NMR. The proton spectrum of the reaction mixture showed the instantaneous formation of ketene aminal **7a** (characteristic signals at $\delta_H$ 4.99 (slightly br t, $J$ = 6.2, 6-H), 3.62 (br t, $J$ = 6, 9-H or 11-H), 3.05 (m, 2-H), 2.99 (m, 9-H or 11-H), 2.11 (pseudo-quartet, $J$ = 6, 5-H); the remaining absorptions of **7a** were masked by other signals) and the resonances of DBU/DBU·HCl ($\delta_H$ 2.85 (m, 6-H), 3.27 (t, $J$ = 6, 9-H), 3.34 (t, $J$ = 6, 11-H), 3.39 (m, 2-H), 11.16 (s br, NH); the other signals at higher field overlapped with the resonances of **7a** and (**8a**)Cl), in addition to the signals of pyrrole ($\delta_H$ 6.14 (q, $J$ = 2.0, $H_\beta$), 6.76 (q, $J$ = 2, $H_\alpha$), 9.34 (br s, NH)) and unreacted (**8a**)Cl ($\delta_H$ 1.74 (unresolved br, 3-H, 4-H, 5-H), 2.20 (quint, $J$ = 6, 10-H), 3.24 (unresolved br, 6-H), 3.80 (t, $J$ = 6.2, 9-H or 11-H), 3.96 (unresolved br, 2-H), 4.11 (pseudo-t, $J$ = 6, 9-H or 11-H), 7.13 (dm, $H_{ortho}$), 7.26 (m, $H_{para}$), 7.38 (m, $H_{meta}$)).[26b] A triplet of very low intensity at 6.28 ppm ($J$ = 2), assigned to the $H_\beta$ protons of **4**,[5,19a] was distinguishable in the spectrum after a few hours (3.5 h). The other proton resonances of **4** were masked by the other signals in the aromatic region. The intensity of this triplet increased slowly in the long run. The formation of **4** was further confirmed by GC and GC/MS (*m*/*z* (EI) 187 ($M^+$), 143, 115, 94, 77, 66, 51, 39).

### Reaction of 7b with pyrrole

Pyrrole (34 μL; 0.490 mmol) was added to a $CDCl_3$ (1 mL) solution of **7b** (52.4 mg; 0.249 mmol). The mixture was allowed to react at ambient temperature and monitored by means of NMR spectroscopy. In addition to the signals of pyrrole ($\delta_H$ 6.14 (t, $J$ = 2.0, $H_\beta$), 6.72 (t, $J$ = 2, $H_\alpha$), 9.87 (br s, NH)) and **7b** (characteristic signals at $\delta_H$ 4.81 (slightly br t, $J$ = 6.2, 6-H), 3.63 (s, OMe), 3.49 (t, $J$ = 6.6, 9-H or 11-H), 2.99 (m, 2-H), 2.89 (m, 9-H or 11-H), 2.06 (t, $J \approx 6$, 5-H); proton 6-H underwent H/D exchange, under the working conditions), the proton spectrum (400 MHz) showed the progressive increase of the signals due to the formation of 1-methoxycarbonyl pyrrole ($\delta_H$ 7.20 (t, $J$ = 2.2, $H_\alpha$), 6.17 (t, $J$ = 2, $H_\beta$), 3.88 (s, OMe))[19a] and DBU ($\delta_H$ 3.22 (t, 9-H), 3.15 and 3.14 (overlapped signals probably due to 2-H and 11-H), 2.36 (m, 6-H); the other signals at higher field overlapped with the resonances of **7b**). In the $^{13}$C spectrum (100 MHz) the resonances of 1-methoxycarbonyl pyrrole were observed at $\delta_C$ 53.65 (OMe), 112.12 ($C_\beta$), 117.18 ($C_\alpha$), 150.58 (COO). The $^{13}$C spectrum also indicated the presence of partially deuterated DBU, probably formed by H/D exchange with $CDCl_3$.[35] The conversion of **7b** into 1-methoxycarbonyl pyrrole was around 78% after 56 h. The GC/MS analysis of the reaction mixture further confirmed the formation of 1-methoxycarbonyl pyrrole (*m*/*z* (EI) 125 ($M^+$), 90, 80, 66, 59, 55, 53, 42, 39) and partially deuterated DBU (153 *m*/*z*) and **7b** (211 *m*/*z*). The FT-IR spectrum of the deuterochloroform solution showed the characteristic strong absorption of the carbonyl group of 1-methoxycarbonyl pyrrole at 1713 $cm^{-1}$.

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21 The protocol followed to obtain the single points of each curve in Fig. 1–5 has been described in Experimental. The legends of the figures report the mean values of the DPC/HetNH (mol/mol) ratio and/or the DBU load (mol% *vs*. HetNH) which were used in building up each curve.

22 (*a*) The reaction mixture obtained by reacting **1**, DPC and DBU (as for the experimental conditions, see entry 1 in Table 3), after cooling to room temperature, was dissolved in diethyl ether. The solution was washed with distilled water, dried over $MgSO_4$ and concentrated *in vacuo*. Upon addition of *n*-hexane and cooling to 253 K, pure DPC precipitated and was isolated by filtration. The mother liquor and washing solutions were collected and the solvent was evaporated. From the residue, which was fractionated on silica gel with petroleum ether/ethyl acetate (20 : 1 v/v), pure **4** (90% yield) and more DPC (pure) were isolated. The total amount of DPC recovered was equal to 90% of the excess used in the catalytic run (*b*) The reaction mixture obtained by reacting **2**, DPC and DBU (1 : 3.8 : 0.1 mol/mol; 393 K, 12 h), after cooling to room temperature, was dissolved in diethyl ether. The solution was washed with distilled water, dried over $MgSO_4$ and concentrated *in vacuo*. From the residue, which was fractionated on silica gel with petroleum ether/diethyl ether (20 : 1 v/v), pure **5** (76% yield) and DPC (70% of the excess used in the catalytic run) were isolated, besides a few mixed fractions which were not worked up further.

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27 p$K_a$ (in DMSO): pyrrole, 23.0; indole, 20.95, carbazole, 19.9.[28a] p$K_a$ (in $H_2O$): pyrrole, 17.51; indole, 16.97.[28b] p$K_a$ of $DBUH^+$: 13.9 (DMSO);[28c] 13.4–12.9 ($H_2O$).[28d] p$K_a$ of PhOH: 18.0 (DMSO) and 10 ($H_2O$).[28a].

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protonation of the N($sp^2$) atom of DBU and is found around 165 ppm in $DBUH^+$.[26b] Analogously, in the proton spectrum (500 MHz, $(CD_3)_2SO$) of the equimolar mixture, the observed resonances do not show any significant shift with respect to the signals found in the proton spectra of the pure components measured under similar experimental conditions (solvent, concentration, temperature), with the exception of the broad signal assigned to the pyrrole N–H proton, whose resonance is slightly shifted downfield (+0.18 ppm), probably as a consequence of a hydrogen-bond interaction (HetNH···N) between the substrate and the base.[32].


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33 We do not exclude that also (**8a**)OPh, by reacting with the $HetN^-$ anion (eqn (4)), may play some role in the formation of product (see also above, in the main text).

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