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Synthesis of Secondary Amides from *N*-Substituted Amidines by Tandem Oxidative Rearrangement and Isocyanate Elimination

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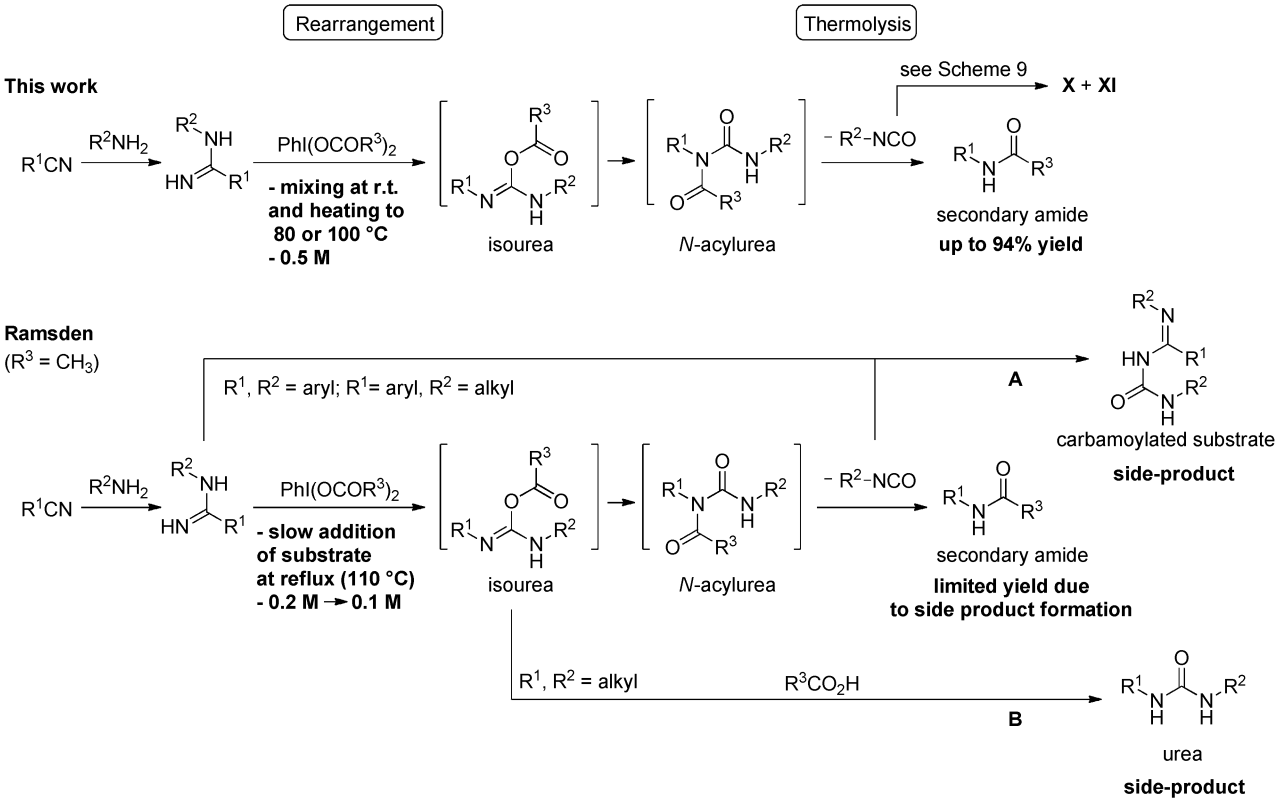
Abstract: In this work an efficient tandem process transforming *N*-substituted amidines into secondary amides has been described. The process involves *N*-acylurea formation by reaction of the substrate with bis(acyloxy)(phenyl)-λ^3-iodane followed by isocyanate elimination. The periodinane reagents are obtained from the commercially available phenyliodine(III) diacetate [$PhI(OAc)_2$, (PIDA)] by ligand exchange with carboxylic acids. The *N*-substituted amidine substrates are easily synthesized from readily available nitriles. The method is applicable for secondary amide synthesis, based on both aliphatic and (hetero)aromatic amines, including challenging amides consisting of sterically hindered acids and amines. Moreover, the protocol allows one to combine steric bulk with electron deficiency in the target amides (aniline based). Such compounds are difficult to synthesize efficiently based on classical condensation reactions involving carboxylic acids and amines. Overall, the synthetic protocol transforms a nitrile into a secondary amide in both aliphatic and (hetero)aromatic systems.

Keywords: amide synthesis; elimination; hypervalent iodine compounds; oxidative rearrangement

Introduction

Amides are important structural motifs in pharmaceuticals, agrochemicals and materials.[1] Nevertheless, the development of efficient methods to synthesize this functional group class remains an important challenge in synthetic organic chemistry.[2] Although amides are the most frequently synthesized functional groups in the pharmaceutical process industry, the methods used to construct them mainly rely on condensation approaches and still involve reagents with poor atom economy.[2b] Classically, secondary amides can be synthesized, starting from the corresponding amines by reaction with carboxylic acid derivatives such as anhydrides and acid chlorides or with carboxylic acids with the aid of coupling reagents.[3] For sterically hindered amides these stoichiometric reagents often just fail. Recently, new synthetic approaches that do not require activation of the carboxylic acid with a stoichiometric reagent, based on a Lewis acid (e.g., boronic acids) or silica as catalyst were developed.[4,5] Catalyst poisoning as well as substrate scope are the main challenges remaining in this attractive approach. It is also possible to make secondary amides from functionalized aldehydes and primary amines with catalytic amounts of an *N*-heterocyclic carbene.[6] Another method is the acylation of primary amines with alcohols or aldehydes, such as the ruthenium-catalyzed amide formation from amines and alcohols described by Milstein.[5,7] Transition metal-catalyzed transformations of nitriles into secondary amides using alcohols, alkyl halides or primary amines and water have also been described.[5,8] Alternatively, secondary amides can be obtained starting from a primary amide *via* alkylation with alkyl halides or arylation with aryl halides under transition metal catalysis.[5,9] Although the latter protocols are very effective under relatively mild conditions, they start from a preformed amide as reagent. Other transition metal-catalyzed approaches based on aryl halides involve the use of carbon monoxide and amines.[5,10] Hence, there is still a huge interest in the development of new and efficient secondary amide syntheses involving the construction of the C(sp^2)–nitrogen bond. In the 1990s Ramsden and co-workers have described the phenyliodine(III) diacetate (PIDA)-mediated oxidative rearrangement of *N*-substituted ami-

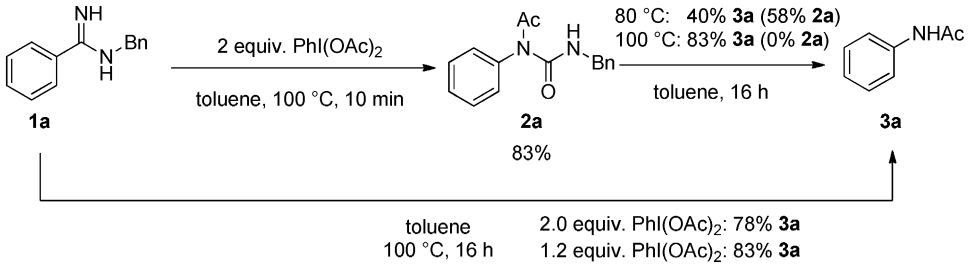


Scheme 1. Transformation of aliphatic and aromatic nitriles into secondary amides.

dines.[11] They observed that the product of the reaction of *N*-substituted amidines with PIDA is determined by the nature of the amidine substituents. *C*-Alkyl-*N*-arylamidines cyclize with formation of 1*H*-benzimidazoles, while *C,N*-dialkylamidines, C,*N*-diarylamidines and *C*-aryl-*N*-alkylamidines under similar reaction conditions undergo an aza-Hofmann rearrangement to give *N*-acetylureas. By elimination of isocyanate, secondary acetamides were obtained. However, the yields were limited to maximum 50% for *C*-aryl-*N*-alkylamidines and *C*,*N*-diarylamidines due to a competitive reaction of isocyanate with substrate (*N*′-carbamoylated *N*-substituted amidine formation) (Scheme 1, A).[12] In the case of *C*,*N*-dialkylamidines, a competitive reaction of isourea with acetic acid gives urea as major compound, also significantly reducing the yield of the acetamides (Scheme 1, B). Encouraged by these preliminary results, and taking into account the interest in alternative amide syntheses, we wondered whether the Ramsden protocol can be transformed into a general high yielding tandem process allowing the efficient and direct transformation of *N*-substituted amidines (both benzenecarboximidamide and alkancarboximidamide) into the corresponding secondary amides without side-product formation (Scheme 1). We found that by changing the way the experiment is executed this can be achieved. By using other hypervalent iodine reagents than PIDA, although not investigated yet, also other amides than secondary acetamides should be accessible. The required bis(acyloxy)(phenyl)-λ^3-iodanes can be easily obtained by an exchange reaction of the acetate groups in PIDA with carboxylic acids.[13] The *N*-substituted amidine substrates are easily accessible from nitriles *via* the corresponding imidate salts (Pinner reaction) or *via* a direct approach using activation by Lewis acids.[14] As aliphatic and aromatic nitriles are readily available commercially or through synthesis,[15] such an approach would deliver a general way to access secondary amides from nitriles[8] and hypervalent iodine reagents (Scheme 1). The process should also allow one to obtain challenging amides based on hindered carboxylic acids or bulky or electron-deficient amines. It is well known that these cannot be obtained efficiently through classical condensation and to the best of our knowledge only one method based on isocyanates and Grignard reagents has described such challenging examples.[16]

Results and Discussion

N-Benzylbenzamidine (**1a**) was selected as model substrate. When **1a** was heated with 2 equiv. PIDA in toluene at 100 °C full conversion was obtained in only



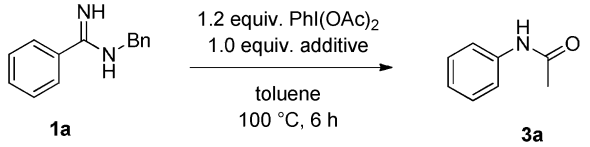
Scheme 2. Acetanilide synthesis optimization.

10 min and 83% of *N*-(benzylcarbamoyl)-*N*-phenylacetamide (**2a**) could be isolated (Scheme 2). When **2a** was heated in toluene at 80 °C for 16 h elimination of benzyl isocyanate occurred and 40% of *N*-acylaniline (**3a**) was isolated, while 58% of the starting material **2a** could be recovered (Scheme 2). When the elimination reaction was performed at 100 °C, full conversion was achieved in an overnight reaction (16 h) with a yield of 83% of **3a**. To investigate if the amidine **1a** could be transformed into the acetanilide **3a** in a tandem process, reaction from **1a** was done overnight (16 h) at 100 °C. Interestingly full conversion of substrate **1a** and intermediate **2a** to acetanilide **3a** was observed and the anilide was isolated in 78% yield. Use of different amounts of PIDA at 100 °C indicated that 1.2 equivalents of PIDA were sufficient (Scheme 2).

Next, we turned our attention to the influence of base and acid additives on the tandem reaction (Table 1). When no additive was added, the NMR yield of the reaction after 6 h was 83% (74% isolated yield) (entry 1). When acetic acid was added, a similar yield and conversion was achieved in the same time (entry 2). On the other hand, Cs_2CO_3 was not beneficial as an additive as only 42% NMR yield of target compound was observed (entry 3). Interestingly, $PhNH_2$ inhibited the reaction (entry 4). PIDA presumably reacts with $PhNH_2$ before it can react with the amidine. Oxidations of aromatic amines with PIDA are known in the literature.[17] Addition of NEt_3 (entry 5) gave a similar result as observed with Cs_2CO_3 (see the Supporting Information for details).

Subsequently, the scope of the method was studied. First the compatibility with substituents in the phenyl ring of the *N*-benzylbenzamidine was investigated (Table 2). Both electron-donating (entries 2 to 8) and electron-withdrawing (entries 9 to 18) substituents are

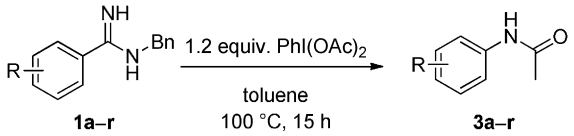
Table 1. Effect of additives on the tandem oxidative rearrangement and isocyanate elimination of **1a**.



Entry	Additive	NMR yield [%][a]	Conversion [%][c]
1	None	83[b]	88
2	AcOH	84	86
3	Cs_2CO_3	42	98
4	$PhNH_2$	3	8
5	Et_3N	45	100

[a] *Reaction conditions:* 0.5 mmol substrate, 1.2 equiv. PIDA, 1.0 equiv. additive, 1 mL toluene, 100 °C, 6 h, argon atmosphere. 1,3,5-Trimethoxybenzene was used as an internal standard.
[b] Isolated yield was 74%.
[c] Based on the consumption of **1a**.

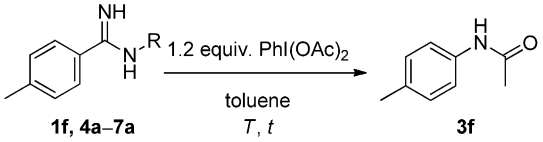
Table 2. Substituent scope in the aryl ring of the *N*-benzylbenzamidine (**1**).



Entry	Substrate	R	Product	Yield [%][a]
1	**1a**	H	**3a**	83[b]
2	**1b**	*p*-OMe	**3b**	80
3	**1c**	*m*-OMe	**3c**	84
4	**1d**	*p*-OEt	**3d**	94
5	**1e**	*p*-SMe	**3e**	78
6	**1f**	*p*-Me	**3f**	85
7	**1g**	*m*-Me	**3g**	66
8	**1h**	*o*-Me	**3h**	70
9	**1i**	*p*-I	**3i**	68
10	**1j**	*p*-Br	**3j**	66
11	**1k**	*m*-Br	**3k**	72
12	**1l**	*o*-Br	**3l**	70
13	**1m**	*p*-Cl	**3m**	72
14	**1n**	*o*-Cl	**3n**	68
15	**1o**	*p*-F	**3o**	68
16	**1p**	*p*-CF_3	**3p**	71
17	**1q**	*m*-CF_3	**3q**	70
18	**1r**	*p*-CO_2Et	**3r**	78

[a] *Reaction conditions:* 0.5 mmol substrate, 1.2 equiv. PIDA, 1 mL toluene, 100 °C, 15 h, argon atmosphere.
[b] 89% of the theoretically formed PhI (calculated for 1 equiv. PIDA) was recovered.

Table 3. Effect of the *N*-alkyl group on the tandem oxidative rearrangement and isocyanate elimination.



1f, 4a–7a **3f**

Entry	Substrate	R	*T* [°C]	*t* [h]	Yield [%][a]
1	**1f**	Bn	100	15	85
2	**4a**	hexyl	100	15	80
3	**5a**	Cy	100	15	90
4	**5a**	Cy	100	5	83
5	**5a**	Cy	80	5	66[b]
6	**6a**	*i*-Pr	100	15	86
7	**6a**	*i*-Pr	100	5	83
8	**7a**	*t*-Bu	100	15	89
9	**7a**	*t*-Bu	100	5	88
10	**7a**	*t*-Bu	80	5	89
11	**7a**	*t*-Bu	60	5	28[c,d]
12	**7a**	*t*-Bu	40	5	11[c,e]

[a] *Reaction conditions:* 0.5 mmol substrate, 1.2 equiv. PIDA, 1 mL toluene, *T*, *t*, argon atmosphere.
[b] 20% of *N*-(cyclohexylcarbamoyl)-*N*-(4-methylphenyl)-acetamide remaining.
[c] NMR yield.
[d] 59% of *N*-(*tert*-butylcarbamoyl)-*N*-(4-methylphenyl)acetamide remaining.
[e] 79% of *N*-(*tert*-butylcarbamoyl)-*N*-(4-methylphenyl)acetamide remaining.

well tolerated and this in *ortho*, *meta* and *para* positions. Even oxidation-sensitive functional groups such as a thiomethyl group (entry 5) were compatible with the reaction conditions.

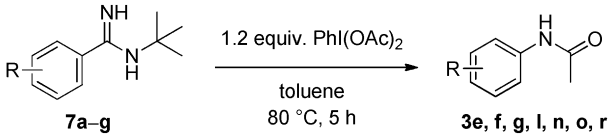
Subsequently, the effect of substitution on the amidine nitrogen was investigated using *para*-toluamidine as template molecule (Table 3). Primary (entries 1 and 2), secondary (entries 3–7) as well as tertiary alkyl groups (entry 8–10) all gave excellent yields. The *N*-*tert*-butyl-*para*-toluamidine (**7a**) reacted significantly faster than the corresponding amidine with an *N*-benzyl substituent as the former already reached full conversion after 5 h (entry 9). Therefore, it was possible to additionally lower the reaction temperature to 80 °C for the tandem protocol (entry 10). Lower reaction temperatures did not give full conversion of the *N*-acetylurea (entries 11 and 12). The *N*-cyclohexyl-*para*-toluamidine (**5a**) also reaches full conversion in 5 h. However at 80 °C, still 20% of *N*-(cyclohexylcarbamoyl)-*N*-(4-methylphenylacetamide was still remaining. As for amide synthesis the amine selected to synthesize the amidine (by reaction with nitrile) will be finally eliminated as an isocyanate, it is not built in the amide reaction product and can therefore be freely selected. Based on the higher reactivity of a *tert*-butyl group it was chosen for further studies.

To confirm that the *tert*-butyl group on nitrogen is also compatible with aryl ring substitution in the benzamidine, as was the case for an *N*-benzyl (Table 2), several functional groups were rescreened (Table 4). Interestingly, at least similar (entries 1, 2, 7) but often higher (entries 3–6) yields were achieved in a shorter reaction time at a lower temperature.

With **7a** other solvents were tested to perform the tandem reaction (Table 5). The reaction gave similar results when 2-methyltetrahydrofuran and *n*-butyl acetate (entries 2 and 3) were used, which is interesting as these solvents are considered to be environmentally benign.[20] The reaction also proceeded in DMSO, with a slight drop in yield to 64% (entry 4). However, the reaction did not work well in ethanol, with a yield of only 31% and some remaining substrate (entry 5).

When a *C*,*N*-diarylamidine was used, as exemplified by *N*-(4-chlorophenyl)benzamidine (**8a**), a mixture of two acetanilides was obtained and no formation of 2-

Table 4. Substituent scope in the aryl ring of the *N*-*tert*-butylbenzamidine **7**.

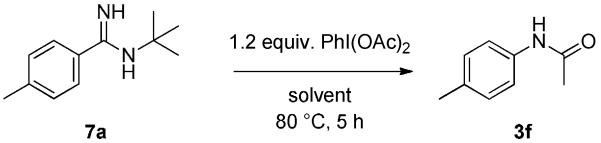


7a–g **3e, f, g, l, n, o, r**

Entry	Substrate	R	Product	Yield [%][a]
1	**7b**	*p*-SMe	**3e**	72
2	**7a**	*p*-Me	**3f**	89
3	**7c**	*m*-Me	**3g**	86
4	**7d**	*o*-Br	**3l**	89
5	**7e**	*o*-Cl	**3n**	87
6	**7f**	*p*-F	**3o**	89
7	**7g**	*p*-CO_2Et	**3r**	81

[a] *Reaction conditions:* 0.5 mmol substrate, 1.2 equiv. PIDA, 1 mL toluene, 80 °C, 5 h, argon atmosphere.

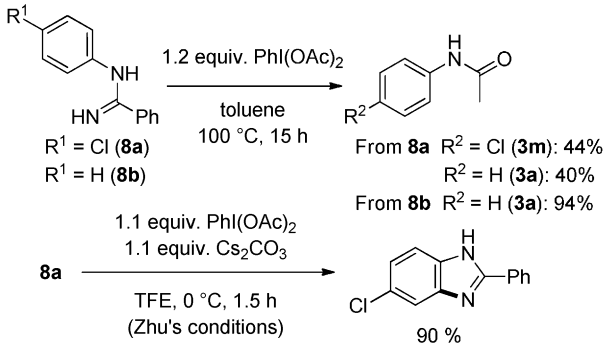
Table 5. Solvent compatibility on the tandem oxidative rearrangement and isocyanate elimination of **7a**.



7a **3f**

Entry	Solvent	Yield [%][a]
1	toluene	89
2	Me-THF	89
3	*n*-BuOAc	78
4	DMSO	64
5	EtOH	31

[a] *Reaction conditions:* 0.5 mmol substrate, 1.2 equiv. PIDA, 1 mL solvent, 80 °C, 5 h, argon atmosphere.



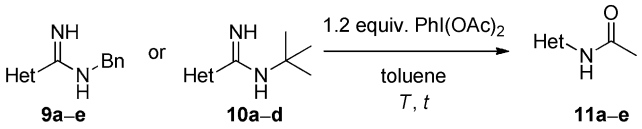
Scheme 3. Reaction of *N*-(4-chlorophenyl)benzamidine (**8a**) and *N*-phenylbenzamidine (**8b**) with PIDA.

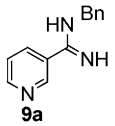
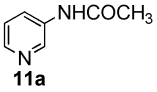
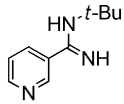
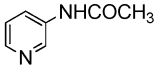
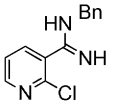
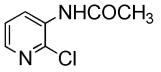
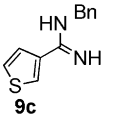
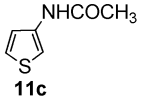
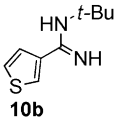
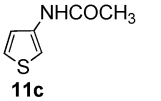
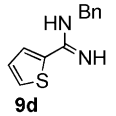
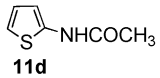
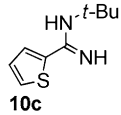
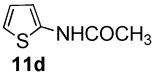
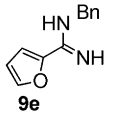
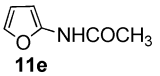
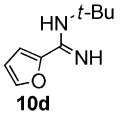
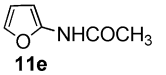
phenyl-5-chloro-1*H*-benzimidazole was observed (Scheme 3). Only when the *C*,*N*-diarylamidine (**8b**) is symmetrical, one reaction product can be obtained (**3a**). In 2012, Zhu reported selective 2-phenyl-5-chloro-1*H*-benzimidazole formation from **8a** by PIDA promotion.[18] Tandem oxidative rearrangement and isocyanate elimination versus direct C(sp^2)–H amidation therefore seems to depend on the solvent selected. As 2,2,2-trifluoroethanol (TFE) promotes radical reactions, it explains the solvent dependent selectivity. For *C*,*N*-diarylamidines Ramsden observed formation of acetanilide and carbamoylated substrate as side product. We did not observe the latter product under our reaction conditions.

Up to this point, only *N*-substituted benzamidines were used as substrates for the tandem protocol. Therefore both *N*-benzyl- and *N*-*tert*-butyl-heteroarene analogues of benzamidines were tested (Table 6). Both pyridine- (**9a**, **10a**, **9b**) (entries 1–3) and thiophene-carboximidamides (**9c**, **10b**, **9d**, **10c**) (entries 4–7) were screened and gave high yields of the target compounds. For furans (**9e**, **10d**) moderate yields were obtained (entries 8 and 9). As aminofurans and aminothiophenes are unstable, a synthetic approach to obtain them in a protected form is interesting.[21] Moreover, these electron-rich systems are also challenging as they could potentially react with the oxidant in a competitive reaction.

Next, the use of other hypervalent iodine compounds than PIDA was tested as this would deliver other amides than those based on acetic acid and therefore broaden the scope of the methodology (Table 7). These hypervalent iodine compounds were easily prepared by an exchange reaction on PIDA with the respective carboxylic acid.[13,22] Subsequently, they were tested in a reaction with **7a** as model substrate (Table 7). The reaction with bis[(2,2-dimethylpropanoyl)oxy]-(phenyl)-λ^3-iodane gave 93% of *N*-pivaloyl-*para*-toluidine (**12a**) (entry 2). Similarly, an isobutyroyl could be smoothly introduced (entry 3). Besides alkanecarboxylic acids, benzoic acids also can be used as exemplified by *N*-benzoyl-*para*-toluidine (**12c**) synthesis from **7a** and bis(benzoyloxy)(phenyl)-λ^3-iodane (entries 4 and 5). Interestingly, sterically hindered carboxylic acids such as 2,4,6-trimethylbenzoic acid can also be used (entries 6 and 7). When bis(2,2,2-trifluoroacetoxy)(phenyl)-λ^3-iodane (PIFA) (entry 8) and bis(2,2,2-trichloroacetoxy)(phenyl)-λ^3-iodane (entry 9) were used, the trihaloacetanilides

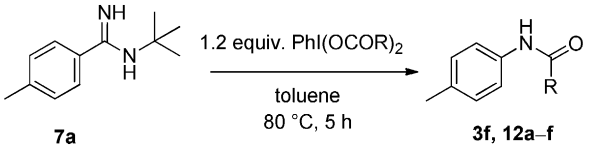
Table 6. Tandem oxidative rearrangement and isocyanate elimination of *N*-benzyl- **9** and *N*-*tert*-butyl-heteroarenecarboximidamides **10**.



Entry	Substrate	Product	*T* [°C]	*t* [h]	Yield [%][a]
1	 **9a**	 **11a**	100	15	83
2	 **10a**	 **11a**	80	5	90
3	 **9b**	 **11b**	100	15	85
4	 **9c**	 **11c**	100	15	74
5	 **10b**	 **11c**	80	5	81
6	 **9d**	 **11d**	100	15	71
7	 **10c**	 **11d**	80	5	70
8	 **9e**	 **11e**	100	15	49
9	 **10d**	 **11e**	80	5	58

[a] *Reaction conditions:* 0.5 mmol substrate, 1.2 equiv. PIDA, 1 mL toluene, *T*, *t*, argon atmosphere.

Table 7. Hypervalent iodine reagent scope.



7a **3f, 12a–f**

Entry	Oxidant	Product	Yield [%][a]
1	$PhI(OAc)_2$	**3f**	89
2	$PhI(OPiv)_2$	**12a**	93
3	$PhI[OCOCH(CH_3)_2]_2$	**12b**	57
4	$PhI(OBz)_2$	**12c**	61[b]
5	$PhI(OBz)_2$	**12c**	73[c]
6	$PhI(OCOMes)_2$	**12d**	45
7	$PhI(OCOMes)_2$	**12d**	46[c]
8	$PhI(OCOCF_3)_2$	**12e**	0
9	$PhI(OCOCl_3)_2$	**12f**	0

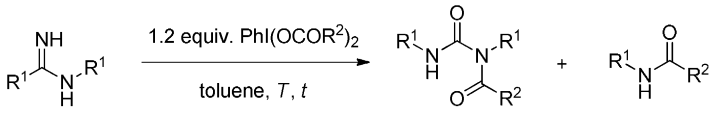
[a] *Reaction conditions:* 0.5 mmol substrate, 1.2 equiv. hypervalent iodine compound, 1 mL toluene, 80 °C, 5 h, argon atmosphere.
[b] 16% of *N*-(*tert*-butylcarbamoyl)-*N*-(4-methylphenyl)benzamide remained.
[c] The reaction was carried out at 100 °C during 15 h.

were not formed. Instead, the trihaloacylated *N*-*tert*-butyl-*para*-toluamidines could be detected by LC-MS analysis of the reaction mixture, together with remaining substrate. Apparently, when the carbonyl of the hypervalent iodine species is too electrophilic, the amidine will perform a nucleophilic attack on the carbonyl group, instead of a nucleophilic attack on the iodine atom.

Besides benzamidines, the suitability of *C*,*N*-dialkylamidines as substrates was also investigated (Table 8). When *N*-benzyl-2-phenylacetimidamide (**13a**) was used as a substrate in a reaction with 1.2 equivalents of PIDA in toluene at 100 °C during 15 h, 82% of *N*-benzylacetamide (**15a**) could be isolated (entry 1). With *N*-cyclohexylcyclohexane-carboximidamide (**13b**) as a starting material under the same reaction conditions, 92% of *N*-cyclohexylacetamide (**15b**) was obtained (entry 2). When the sterically hindered *N*-*tert*-butyl-2,2-dimethylpropanimidamide (**13c**) was tested under the reaction conditions for *N*-*tert*-butylbenzamidines (80 °C, 5 h), oxidative rearrangement into *N*-acyl-*N*,*N*′-di-*tert*-butylurea (**14c**) occurred by reaction with PIDA but no subsequent elimination occured (entry 3). Applying the reaction conditions optimized for *N*-benzylbenzamidines (100 °C, 15 h) already gave 13% of the desired *N*-acyl-2,2-dimethylpropanamide (**15c**), but still 59% of **14c** remained (entry 4). Increasing the reaction temperature further to 130 °C allowed one to completely and efficiently convert *N*-acetyl-*N*,*N*′-di-*tert*-butylurea into the target compound **15c** (entry 6). Attempts to use additives to speed up the *tert*-butyl isocyanate elimination on **14c** were unsuccessful. At 0 °C, alcoholates like LiOBn and NaOMe led to formation of the 1,3-di-*tert*-butylurea.[23] Lewis acids either led to decomposition ($AlCl_3$, $FeCl_3$, $ZnBr_2$) or formation of acetamide ($GaCl_3$, $CuBr_2$). Only $Zr(acac)_4$ gave 67% of the desired compound, but also 32% of 1,3-di-*tert*-butylurea (see the Supporting Information for details). Brønsted acids either also led to decomposition (benzenesulfonic acid) or left the *N*-acylurea **14c** unreacted.

The sterically hindered **13c** was also tested in combination with other periodinanes (Table 8). With bis[(2,2-dimethylpropanoyl)oxy](phenyl)-λ^3-iodane as oxidant 2,2-dimethylpropanoyl-2,2-dimethylpropanamide (**15d**) was obtained in a good yield (entries 8 and 9). Also, the reaction with bis(benzoyloxy)(phenyl)-λ^3-iodane gave the target amide **15e** but in a moderate yield (entry 10). For *C*,*N*-dialkylamidines,

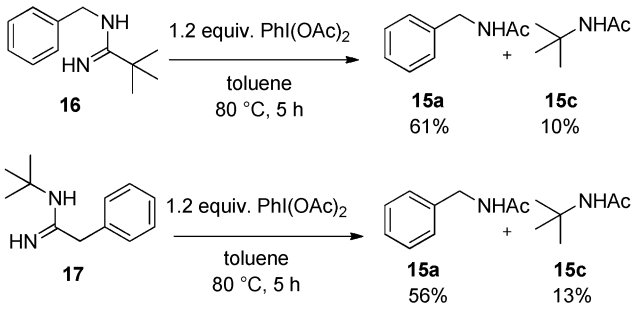
Table 8. Tandem oxidative rearrangement and isocyanate elimination of *C*,*N*-dialkylamidines **13**.



13a–c **14a–e** **15a–e**

Entry	Substrate	R^1	Oxidant	R^2	*T* [°C]	*t* [h]	*N*-Acylurea	Yield [%]	Product	Yield [%][a]
1	**13a**	Bn	$PhI(OAc)_2$	Me	100	15	**14a**	0	**15a**	82
2	**13b**	Cy	$PhI(OAc)_2$	Me	100	15	**14b**	0	**15b**	92
3	**13c**	*t*-Bu	$PhI(OAc)_2$	Me	80	5	**14c**	62	**15c**	0
4	**13c**	*t*-Bu	$PhI(OAc)_2$	Me	100	15	**14c**	59	**15c**	13
5	**13c**	*t*-Bu	$PhI(OAc)_2$	Me	120	6	**14c**	62	**15c**	9
6	**13c**	*t*-Bu	$PhI(OAc)_2$	Me	130	6	**14c**	0	**15c**	77
7	**13c**	*t*-Bu	$PhI(OAc)_2$	Me	140	6	**14c**	0	**15c**	72
8	**13c**	*t*-Bu	$PhI(OPiv)_2$	*t*-Bu	140	6	**14d**	0	**15d**	84
9	**13c**	*t*-Bu	$PhI(OPiv)_2$	*t*-Bu	140	2.5	**14d**	0	**15d**	86
10	**13c**	*t*-Bu	$PhI(OBz)_2$	Ph	140	2.5	**14e**	0	**15e**	48

[a] *Reaction conditions:* 0.5 mmol substrate, 1.2 equiv PIDA, 1 mL toluene, *T*, *t*, argon atmosphere.

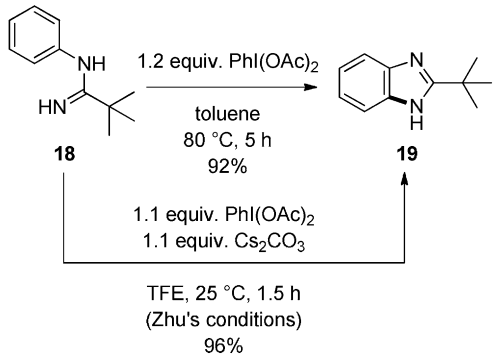


Scheme 4. Reaction of isomeric C,*N*-dialkylamidines **16** and **17** featuring two different alkyl groups.

Ramsden observed formation of ureas. Our protocol prevents formation of this side product and consequently gives high yields of secondary amides. This can be demonstrated with **13b**, which is one of the amidines that was also tested by Ramsden. Under their conditions, *N*-cyclohexylacetamide (**15b**) (32%), *N*,*N*′-dicyclohexylurea (28%) and *N*-acetyl-*N*-*N*′-dicyclohexylurea (21%) were formed, while we obtained 92% of **15b**.

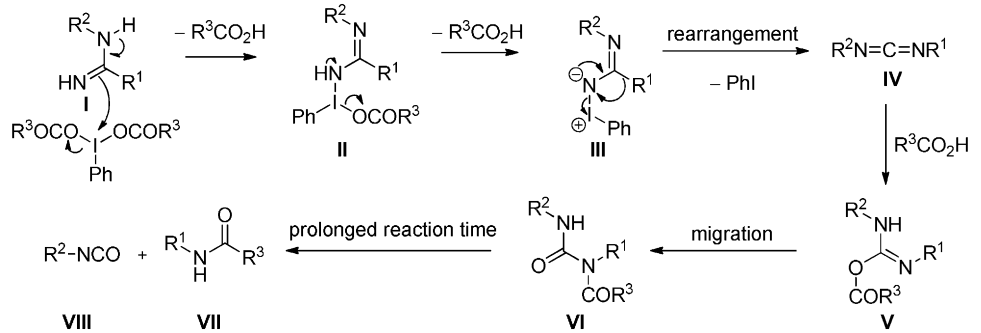
When *C*,*N*-dialkylamidines with two different alkyl groups were selected, mixtures of *N*-acetylalkanamines were formed. Reaction of *N*-benzyl-2,2-dimethylpropanimidamide (**16**) with PIDA at 80 °C during 5 h yielded 61% of **15a** together with 10% of **15c** (Scheme 4). Interestingly, with *N*-*tert*-butyl-2-phenylethanimidamide (**17**), in which both alkyl groups are switched, the same products were obtained in similar yields. Although the selection of the sterically hinderd *tert*-butylamine to synthesize *C*,*N*-dialkylamidine from aliphatic nitriles will allow one to achieve the *N*-acylalkanamine based on the C-subsituent of the amidine as the major reaction product, *C*,*N*-dialkylamidines featuring the same alkyl group will allow one to generate only one *N*-acylalkanamine and are therefore preferred (Table 8).

With a *C*-alkyl-*N*-arylamidine as substrate only 1*H*-benzimidazole was formed as was observed by Ramsden. Reaction of 2,2-dimethyl-*N*-phenylpropanimidamide with PIDA under the optimal reaction conditions gave 92% of 2-*tert*-butyl-1*H*-benzimidazole. This yield is similar to the one obtained under the reaction conditions of Zhu (Scheme 5).[18]

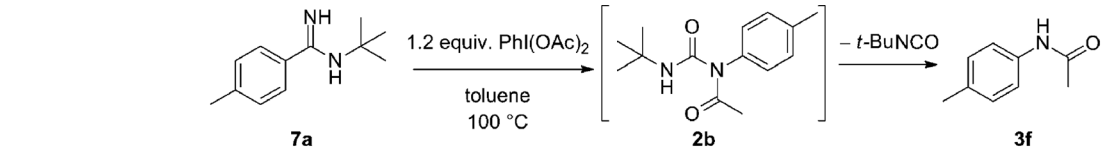


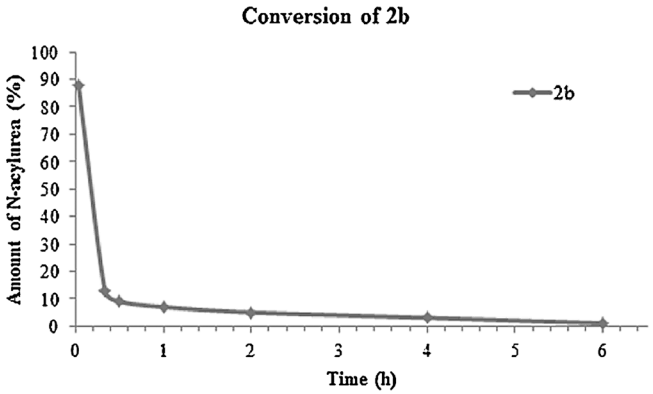
Scheme 5. Synthesis of 1*H*-benzimidazole **19** from *C*-alkyl-*N*-arylamidine **18**.

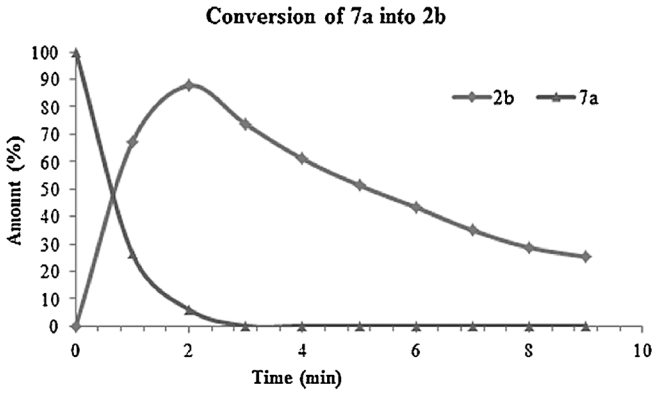
A possible mechanism for this transformation is shown in Scheme 6.[11b] The substrate **I** reacts with hypervalent iodine reagent *via* its unsubstituted nitrogen. Subsequently, this *N*-activated compound **II** eliminates carboxylic acid resulting in an ylide **III** which rearranges to a carbodiimide **IV** with concomitant formation of iodobenzene. Protonation of the carbodiimide by carboxylic acid, followed by nucleophilic attack of the carboxylate on the carbodiimidium leads to the formation of an isourea **V** which subsequently undergoes spontaneous *O*- to *N*-acyl migration, thereby yielding an *N*-acylurea **VI**. Subsequently, elimination of isocyanate **VIII** from **VI** occurred yielding secondary amide **VII**.[11b] The basicity of the nitrogen atoms of the carbodiimide **IV** determines the selectivity of the reaction. In case of *C*-aryl-*N*-alkylamidines, an *N*-aryl-*N*′-alkylcarbodiimide is formed and protonation will always occur on the more basic alkylimine moiety, thereby regioselectively giving access to anilides. In the case of *C*,*N*-diarylamidines and *C*,*N*-dialkylamidines carbodiimides with respectively two aryl or two alkyl groups on nitrogen are formed. As the



Scheme 6. Proposed reaction mechanism for the tandem oxidative rearrangement and isocyanate (**VIII**) elimination of *N*-substituted amidines (**I**).[11b]

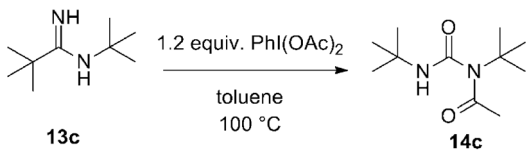


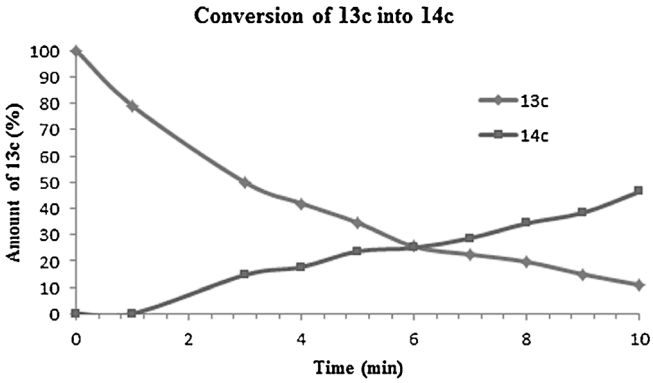




Scheme 7. Conversion of **7a** and **2b** as a function of time.

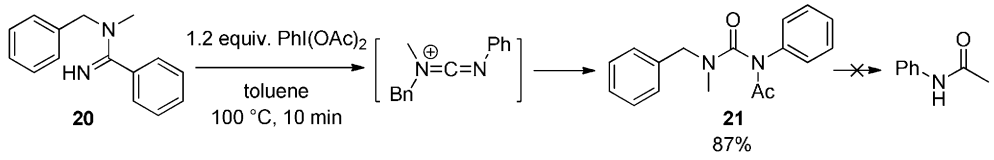
basicity of both nitrogen atoms becomes very similar mixtures of amides are expected. This was observed for *N*-(4-chlorophenyl)benzamidine (**8a**) featuring two different aryl groups (Scheme 3). Also, steric factors play a role in such cases as acyl migration will preferentially occur to the less sterically hindered nitrogen. This is supported by the reactions starting from isomeric *C*,*N*-dialkylamidines **16** and **17** delivering the same reaction mixture irrespective of the substrate (Scheme 4). A kinetic analysis as function of time of the tandem reaction starting from **7a** revealed that the starting material is very quickly converted to *N*-acylurea intermediate **2b** (around 2 min) while isocyanate elimination is slower (Scheme 7). The observation that tertiary alkyl substituents give a faster reaction than secondary and primary alkyl substituents in *N*-alkylamidines therefore seems to be linked to an easier elimination of tertiary isocyanates from *N*-acylurea (**VI**) (Table 3). For **13c**, the same kinetic analysis was done (Scheme 8). In this case the starting material is consumed more slowly. Migration of an alkyl group on carbon seems to be slower than an aryl group. This rationalizes why **8a** and **8b** undergo rearrangement and **18** only yields benzimidazole. To further support this mechanism, an *N*,*N*-disubstituted amidine was used as substrate. After all, the reaction should stop after the rearrangement step as the second substituent prevents elimination of isocyanate. This is demonstrated by the reaction of *N*-benzyl-*N*-methylbenzamidine (**20**) with PIDA at 100 °C where *N*-(*N*′-benzyl-*N*′-methylcarbamoyl)-*N*-phenylacetamide (**21**) is formed in 87% yield. This product was stable towards further heating. In this case the rearrangement goes *via* an *N*-methyl-*N*-benzylcarbodiimidium intermediate (Scheme 9). *N*,*N*-Dialkylcarbodiimidium species are known in the literature and have been obtained *via* alkylation of the corresponding carbodiimides.[24]



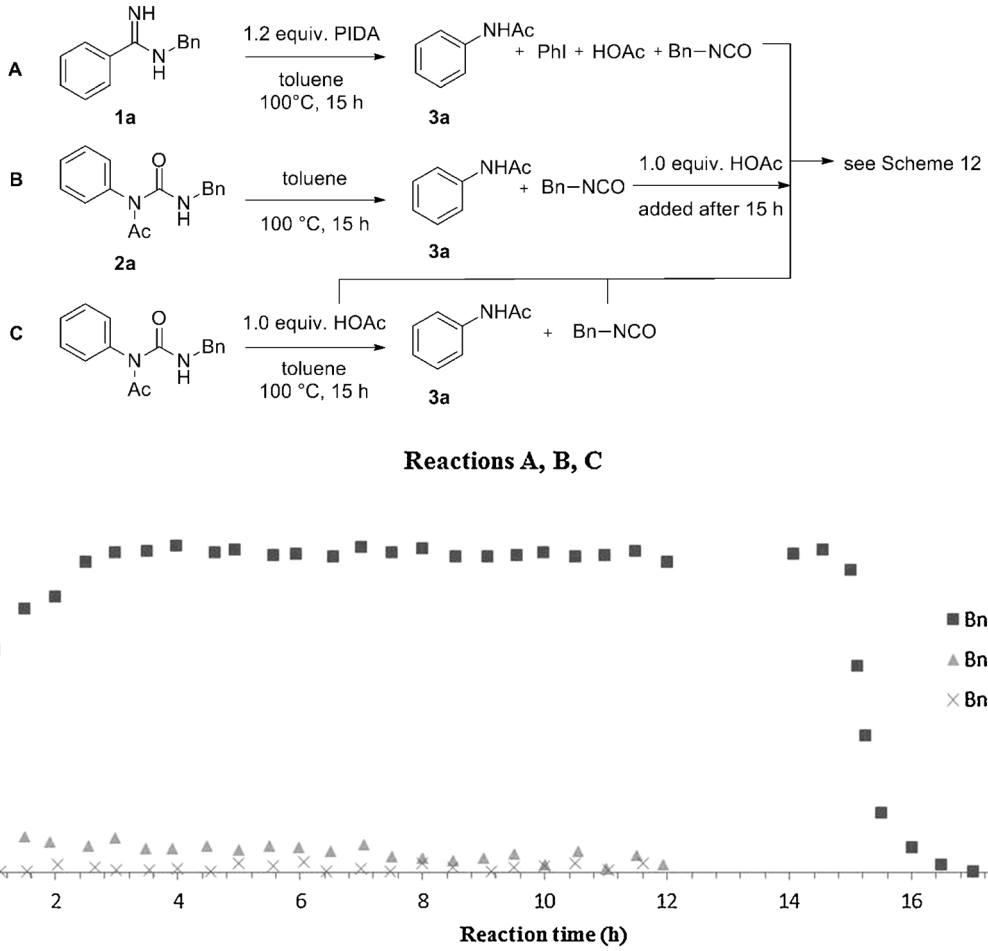


Scheme 8. Conversion of **13c** as a function of time.

As no nucleophile is added to react with the isocyanate formed in the elimination step, we wondered about its final fate in our protocol. In the transformation of *N*-substituted amidine into *N*-acylurea, two equivalents of carboxylic acid are formed. One of these is used to react with the carbodiimide intermediate. However, the other one is not consumed in this process. When elimination of isocyanate occurs the carboxylic acid can react with isocyanate, forming a mixed anhydride of a carboxylic acid and a carbamic



Scheme 9. Reaction of *N,N*-disubstituted amidine **20** with PIDA.

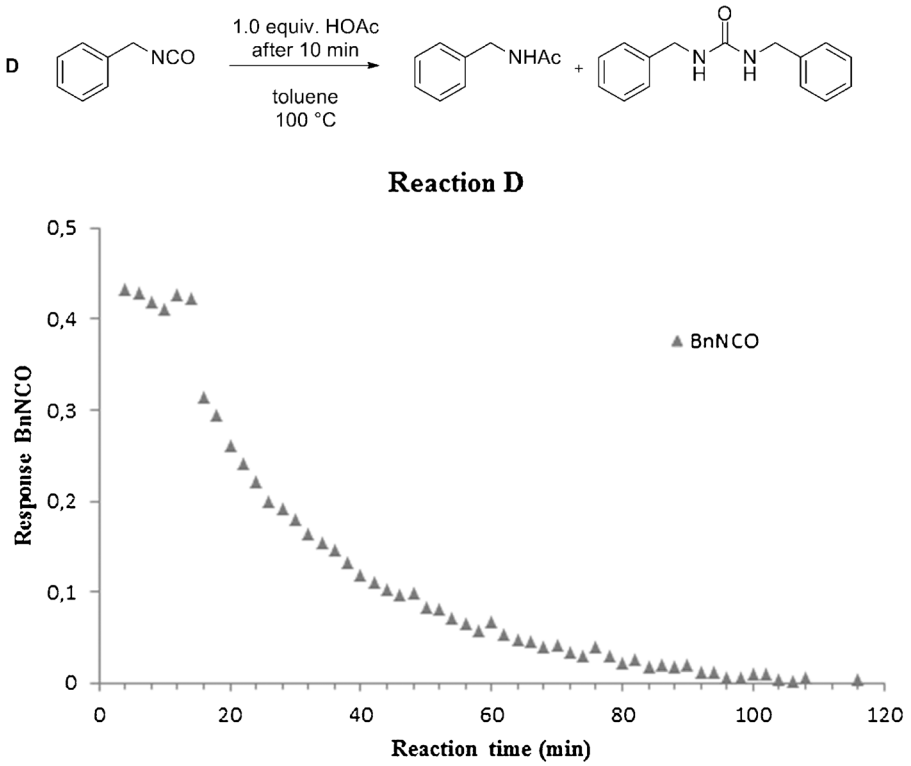


Scheme 10. Detection of benzyl isocyanate with online IR in the reactions starting from **1a** and **2a**.

acid **IX** (Scheme 12). This product is not stable and will lose carbon dioxide directly or *via* reaction with carboxylic acid. Such reactions of isocyanates with carboxylic acid are known in the literature.[11b,25] This can either lead to formation of **X** or towards formation of an amine, which can react with isocyanate **VIII** forming urea **XI**. Analysis of the reaction mixture of **7a** with PIDA (Table 4, entry 2) with LC-MS showed both formation of 1,3-di-*tert*-butylurea (**XI**) and *N*-*tert*-butylacetamide (**X**).

To further support the reaction mechanism, we tried to detect the isocyanate **VIII** with online IR monitoring. Starting from our amidine substrate **1a**, we were not able to detect benzyl isocyanate (Scheme 10, reaction A). However, with intermediate *N*-acetylurea **2a** as substrate benzyl isocyanate (2266 cm^{-1}) was clearly formed (reaction B). When performing the same reaction in the presence of 1 equivalent of acetic acid, no isocyanate could be detected (reaction C). This indicates that the formed isocyanate rapidly reacts with acetic acid, so that it cannot be detected by IR (low concentration). To prove this, in the reaction starting from **2a** acetic acid was added after 15 h (reaction B). As expected, the isocyanate is consumed upon addition of the acid. A reference reaction of benzyl isocyanate with acetic acid confirmed the reaction between both compounds (Scheme 11, reaction D).

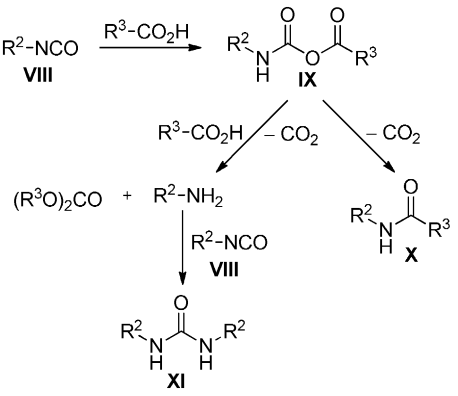
As mentioned previously, when the procedure of Ramsden was used for the synthesis of secondary



Scheme 11. Reaction of benzylisocyanate with acetic acid.

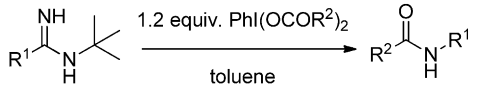
amides, low yields are obtained due to the formation of undesired side products (Scheme 1, A and B). However, with our newly developed reaction protocol no side products were observed in these cases (Scheme 1), with higher yields of the desired secondary amide as a consequence. The different outcome between our protocol and the Ramsden procedure is therefore due to the way in which the reaction is performed. In the case of *C,N*-diarylamidines and *C*-aryl-*N*-alkylamidines, carbamoylated substrate was formed under the Ramsden conditions (Scheme 1, A). The difference can be rationalized by the slow addition of substrate to a refluxing solution of PIDA in toluene *versus* mixing of substrate and reagent at room temperature followed by heating. In the former procedure *N*-acetylurea is gradually formed allowing it to eliminate isocyanate which in a competitive reaction can react with the slowly added substrate. As the rearrangement is very fast, immediate mixing prevents isocyanate elimination when substrate is still present and therefore no side product formation occurs (Scheme 7). For *C,N*-dialkylamidines, undesired urea formation was observed by Ramsden (Scheme 1, B). Here the pH presumably plays a crucial role in the different outcome observed under our reaction conditions. After all, a low *versus* high concentration of amidine will generate a different pH when acetic acid is formed by oxidative rearrangement. The buffering role of substrate under our reaction conditions (high concentration) therefore suppresses the reaction of isourea with acetic acid (Scheme 12).

With all this information in hand, we investigated whether this new method can be used for the synthesis of sterically hindered or electron-deficient secondary amides (Table 9). These are notorious for their difficult synthesis.[2a] Recently, the synthesis of such amides was described starting from Grignard reagents and isocyanates.[16] To synthesize these amides using our method, we first made the *N*-*tert*-butylamidines by reaction of the corresponding nitriles with *tert*-butylamine (see the Supporting Information). Subse-

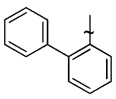
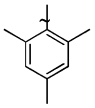
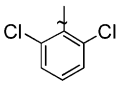
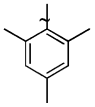
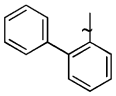
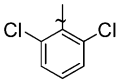


Scheme 12. Possible decomposition pathways for isocyanate (**VIII**).

Table 9. Synthesis of sterically hindered and electron-deficient secondary amides applying the tandem protocol.



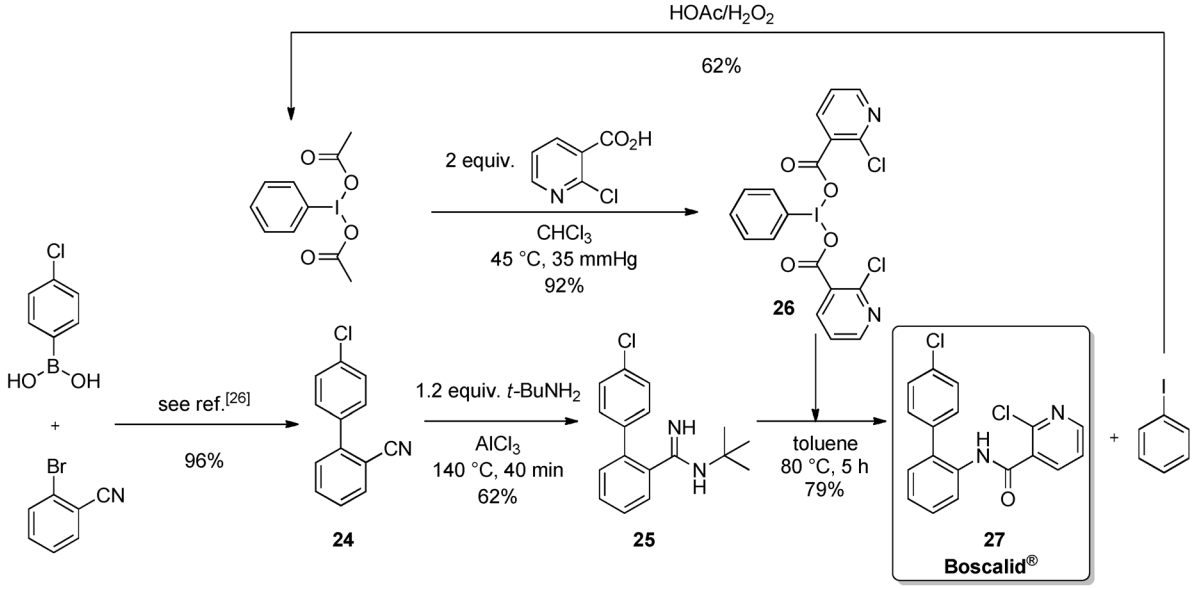
22a, b **23a–d**

Entry	Substrate	R^1	R^2	Product	Yield [%][a]
1	**22a**			**23a**	74
2	**22b**			**23b**	46
3	**22a**			**23c**	87
4	**22b**			**23d**	98

[a] *Reaction conditions:* 0.5 mmol substrate, 1.2 equiv. $PhI(OCOR^2)_2$, 1 mL toluene, 80 °C, 5 h, argon atmosphere.

quently, these amidines were allowed to react with bis[(mesitylcarbonyl)oxy](phenyl)-λ^3-iodane. When *N*-*tert*-butylbiphenyl-2-carboximidamide (**22a**) was used as a substrate, 74% of the corresponding amide could be isolated (entry 1). *N*-Biphenyl-2-ylamides are interesting molecules because they can be used as substrate for the synthesis of carbazoles *via* C–H activation.[26] When *N*-*tert*-butyl-2,6-dichlorobenzamidine (**22b**) was used as substrate, 46% of the corresponding amide was formed (entry 2). The same substrates were also reacted with another sterically hindered periodane, namely bis[(2,2-dimethylpropanoyl)oxy](phenyl)-λ^3-iodane, providing even higher yields than obtained with bis[(mesitylcarbonyl)oxy](phenyl)-λ^3-iodane (entries 3 and 4).

To demonstrate the applicability of the protocol, we subsequently synthesized Boscalid® in an alternative manner (Scheme 13). Chemically seen, the amide is an interesting case as it involves a heteroaromatic carboxylic acid. Boscalid is an important fungicide with an annual production of more than 1000 tons.[27] The required substrate was made in two steps with 60% overall yield.[28] This amidine smoothly undergoes oxidative rearrangement by reaction with **26** and by subsequent elimination Boscalid® (**27**) was obtained in 79% yield after crystallization of the crude reaction product from methanol. We only used 1.0 equivalent of the hypervalent iodine compound **26** which demonstrates that it is not always necessary to use 1.2 equivalents. By washing the crude reaction product several times with heptane, we were able to separate the iodobenzene formed during the reaction, upon reduction of the bis(acyloxy)(phenyl)-λ^3-iodane. Crude iodobenzene could be reused by oxidation into PIDA with hydrogen peroxide and acetic acid.[20b] In this way we were able to recover 62% of the originally used amount of PIDA. The hypervalent iodine **26** could be easily synthesized in high yield from PIDA and 2-chloronicotinic acid. Interestingly, nicotinic acid-based periodinanes are to the best of our knowledge not yet described in literature.



Scheme 13. Synthesis of Boscalid® based on our tandem protocol.

For the substrate on which our optimization was performed (**1a**) separation of iodobenzene was also tested and 89% of the theoretically formed iodobenzene could be recovered (Table 1, entry 1). In this case iodobenzene could be easily separated during the automated column chromatography purification on silica gel. It comes off as the first chromatographic peak when eluting with 100% heptane.

Conclusions

In conclusion, an efficient tandem oxidative rearrangement elimination reaction of *N*-substituted amidines was developed which allows for the synthesis of secondary amides. The amidine substrates are readily available from the corresponding nitriles and the bis(acyloxy)(phenyl)-λ^3-iodanes from PIDA. Both aliphatic as well as aromatic and heteroaromatic nitriles can be used. The protocol can also be applied to synthesize secondary amides composed of sterically hindered carboxylic acids and bulky (electron-deficient) amines. As an application, Boscalid® was synthesized in an alternative manner.

Experimental Section

General Procedure for the Tandem Oxidative Rearrangement Isocyanate Elimination of *N*-Substituted Amidines

An oven-dried microwave vial (10 mL) equipped with a magnetic stirring bar was charged with the *N*-substituted amidine (0.5 mmol) and $PhI(OCOR)_2$ (0.6 mmol). The vessel was flushed with argon for 1 min and then sealed with a crimp cap with septum. 1 mL of dry toluene was added *via* a syringe to the vessel. The reaction mixture was heated at 100 °C and stirred for 15 h for *N*-benzyl-substituted amidines and at 80 °C for 5 h for *N-tert*-butyl-substituted amidines, unless mentioned otherwise. After completion of the reaction, the reaction mixture was allowed to cool down to room temperature and toluene was evaporated under reduced pressure. The crude product was purified by an automated chromatography system using silica flash cartridges.

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14 Synthesis of Secondary Amides from *N*-Substituted Amidines by Tandem Oxidative Rearrangement and Isocyanate Elimination

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