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A mild, expedient, one-pot trifluoromethanesulfonic anhydride mediated synthesis of *N*-arylimidates

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ABSTRACT

The direct transformation of various secondary amides into *N*-arylimidates via mild electrophilic amide activation with trifluoromethanesulfonic anhydride (Tf_2O) in the presence of 2-chloropyridine (2-ClPyr) is described. Low-temperature amide activation followed by C–O bond formation with 2-naphthol provides the desired *N*-arylimidates in short overall reaction times. In contrast, reaction with oxindole proceeds via formation of a C–C bond to give 1-(1*H*-indol-2-yl)naphthalene-2-ol.

N-Arylimidates, serve as starting materials in the Chapman rearrangement for the production of *N*,*N*-diarylamides and polyamides.[1] Therefore, general methods reported for the synthesis of *N*-arylimidates imply the Beckman rearrangement of ketoximes[2] or the addition of phenols to imidoyl chlorides.[3] Another way to synthesize *N*-arylimidates is to react *N*-aryl imidoyl chlorides with an alkoxide anion in THF at reflux with exclusion of moisture under nitrogen.[4] The dehydration of secondary amides to give imidoyl chlorides has traditionally been carried out by heating with reagents such as $SOCl_2$, PCl_5, or $POCl_3$ in excess, or by treatment with Ph_3P/CCl_4 at room temperature.[5] The major drawbacks of these methods are that the excess dehydrating agent and reagent-derived by-products need to be removed. Moreover, the pure imidoyl chlorides are separated either by fractional distillation or precipitation methods under anhydrous conditions. Due to the low reactivity of imidoyl chlorides, stoichiometric amounts of Lewis acids[6] or more nucleophilic phenoxide anions[7] are required. An alternative method for the formation of *N*-arylimidates includes the use of oxalyl chloride as a chlorinating agent in the presence of 2,6-lutidine at 0 °C, which generates the imidoyl chlorides in situ without the formation of by-products.[8]

A nitrilium ion generated as an intermediate under Beckmann rearrangement conditions or via activation of imidoyl chlorides with stoichiometric amounts of Lewis acids plays the key role in the production of *N*-arylimidates. A combination of trifluoromethanesulfonic anhydride (Tf_2O) and pyridine in the pioneering work of Charette and Grenon, in their synthesis of amidines, thiazolines, thioamides, and cyclic orthoesters, has proven to be a useful method for the activation of amides and their subsequent conversion into other functional groups.[9] In 2006, Movassaghi developed an efficient method for the conversion of amides into highly electrophilic 2-chloropyridinium adducts by using a combination of Tf_2O and 2-ClPyr, which enabled the synthesis of a variety of azaheterocycles.[10]

Compared to the reported methods for the synthesis of *N*-arylimidates, we considered that the development of new methodologies would allow the highly effective activation of a variety of amide substrates, including *N*-arylamides, without requiring isolation of sensitive intermediates or the use of Lewis acid additives. Herein, we describe an expedient transformation of various secondary amides into *N*-arylimidates via mild electrophilic amide activation with Tf_2O in the presence of 2-ClPyr.

First we optimized the conditions for the synthesis of naphthalen-2-yl *N*-4-methoxyphenylpivalimidate (**2a**) from *N*-(4-methoxyphenyl)pivalamide (**1a**) and 2-naphthol (Table 1).[11] All analytical data including IR, ^1H and ^{13}C NMR, and the mass fragmentation pattern of **2a**[12] were in agreement with the proposed structure.[13]

2-ClPyr proved to be the best base and gave a 96% yield of the desired product (Table 1, entry 7). While base additives such as triethylamine and pyridine had no effect on the reaction progress (Table 1, entries 3 and 4), other bases activated amide **1a** with moderate efficiencies (Table 1, entries 2 and 5). An excess of 2-ClPyr was found to have a minor inhibitory effect (Table 1, entry 8), perhaps by shifting the equilibrium away from **5**, the more active nitrilium intermediate, toward **4**, the less active amidinium intermediate, in order to counteract the increasing concentration of 2-ClPyr (see Scheme 1).[14] The reaction proceeds with less efficiency when using the Hendrickson reagent[15] (Table 1, entry 6). Therefore, the superiority of the Tf_2O–2-ClPyr combination as an amide activating agent is evident.

We next explored the substrate scope using the optimal conditions with a variety of secondary amides. The results are presented in Table 2 and revealed that substrates with electron-donating as well as electron-withdrawing groups were tolerated in the reactions. While relatively electron-rich pivalamides gave the corresponding products in 94% to 96% yields (Table 2, entries 1, 3

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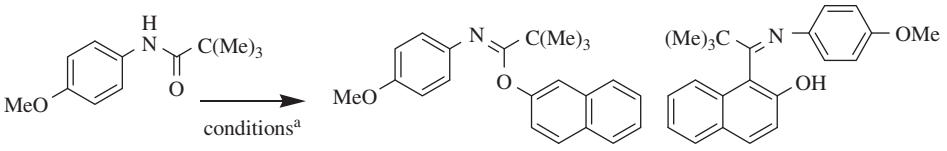
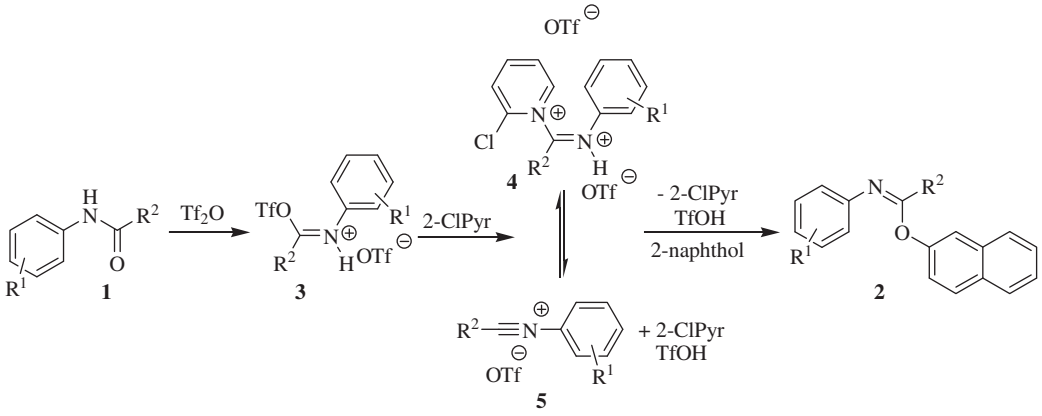
Table 1
Results obtained for the direct conversion of amide **1a** into *N*-arylimidate **2a**



1a **2a** **2a'** (not formed)

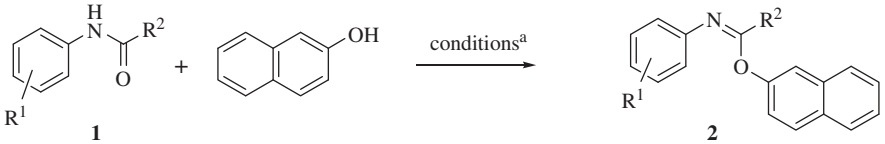
Entry	Base additive	Equiv	Isolated yield (%)
1	None	—	35
2	K_2CO_3	2.0	37
3	Et_3N	1.2	0
4	Pyridine[b]	1.2	0
5	2,6-Lutidine	1.2	73
6	Hendrickson reagent[c]	1.2	61
7	2-ClPyr	1.2	96
8	2-ClPyr	2.0	91

[a] Conditions: amide (1.0 equiv), Tf_2O (1.1 equiv), base, CH_2Cl_2, −78 °C, 5 min, then warmed to 0 °C, 2-naphthol (1.0 equiv), then 25 °C, 3 h.
[b] Naphthalen-2-yl trifluoromethanesulfonate and recovered starting amide were obtained.
[c] Triphenylphosphonium anhydride trifluoromethanesulfonate was used without 2-ClPyr at 0 °C.



Scheme 1. Reaction mechanism for the formation of **2**.

Table 2
Results obtained for the direct conversion of amides **1** into *N*-arylimidates **2a**–**m** via mild electrophilic activation by Tf_2O–2-ClPyr

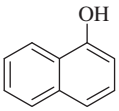
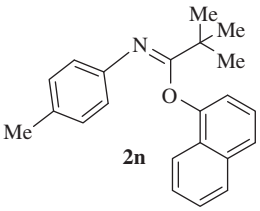
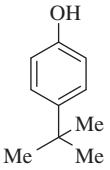
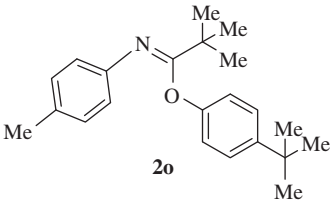
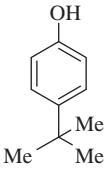
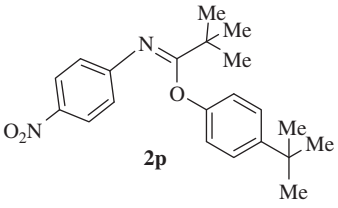


1 **2**

Entry	R^1	R^2	Product	Isolated yield (%)
1	4-MeO-	*tert*-Bu-	**2a**	96
2	H-	*tert*-Bu-	**2b**	93
3	4-Me-	*tert*-Bu-	**2c**	94
4	3-Me-	*tert*-Bu-	**2d**	87
5	3,4-$(Me)_2$-	*tert*-Bu-	**2e**	94
6	4-Cl-	*tert*-Bu-	**2f**	83
7	4-NO_2-	*tert*-Bu-	**2g**	66
8	H-	Cyclohexyl-	**2h**	78
9	4-Me-	Cyclohexyl-	**2i**	80
10	4-MeO-	Cyclohexyl-	**2j**	81
11	H-	Ph-	**2k**	63
12	4-Me-	Ph-	**2l**	66
13	4-Cl-	Ph-	**2m**	58

[a] Conditions: amide (1.0 equiv), Tf_2O (1.1 equiv), 2-ClPyr (1.2 equiv), CH_2Cl_2, −78 °C, 5 min, then warmed to 0 °C, 2-naphthol (1.0 equiv), then 25 °C, 3 h.

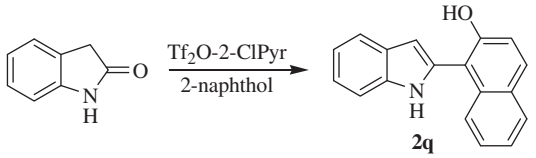
Table 3
Rections of amides **1c** and **1g** with 1-naphthol and 4-*tert*-butylphenol[a]

Entry	Amide	Ar-OH	Product	Isolated yield (%)
1	**1c**		 **2n**	88
2	**1c**		 **2o**	98
3	**1g**		 **2p**	80

[a] Conditions: amide (1.0 equiv), Tf_2O (1.1 equiv), 2-ClPyr (1.2 equiv), CH_2Cl_2, −78 °C, 5 min, then warmed to 0 °C, Ar-OH (1.0 equiv), then 25 °C, 3 h.

and 5), reactions of relatively electron-deficient benzamides proceed to the products less efficiently (Table 2, entries 11, 12, and 13). Cyclohexanecarboxamides with moderate electronic character afforded *N*-arylimidates **2** in 78–81% yields (Table 2, entries 8–10).

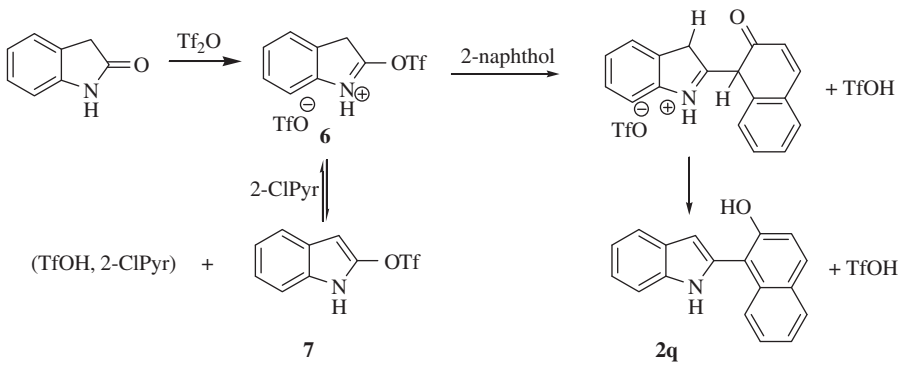
We also examined the effect of 1-naphthol, and 4-*tert*-butylphenol and the results are shown in Table 3. Reactions with 1-naphthol[16] and 4-*tert*-butylphenol[17] proceeded similar to those with 2-naphthol affording the corresponding *N*-arylimidates. It is notable that while relatively electron-rich *N*-*p*-tolylpivalamide gave **2o** in 98% yield, electron-deficient *N*-(4-nitrophenyl)pivalamide afforded **2p** in 80% yield (Table 3, entries 2 and 3).



Scheme 2. Formation of **2q** from oxindole.

To rationalize the results, the pathway depicted in Scheme 1 seems to be operative in our method. Activation of amides **1** affords the *O*-triflylimininium triflate **3**. Addition of 2-ClPyr to **3** then gives the 2-chloropyridinium adduct **4**. Subsequent reaction of 2-naphthol with either **4** or the nitrilium ion **5** affords the *N*-arylimidates **2**.[14] Electron-rich amides with higher propensity to form a nitrilium ion upon activation with the Tf_2O–2-ClPy combination are expected to give the highest yields. On the other hand, electron-deficient amides, which are reluctant to form the corresponding nitrilium ions afford the lowest yields, probably due to the inductive effect of the nitrogen substituent.[13]

Particularly significant is oxindole, reaction of which proceeds by formation of a C–C bond to give 1-(1*H*-indol-2-yl)naphthalen-2-ol (**2q**) in 52% yield under the reported reaction conditions (Scheme 2).[18] We believe that the different behavior of oxindole in comparison to other amides relies on the different intermediates reacting with 2-naphthol (Scheme 3). Activation of oxindole affords the *O*-triflylimininium triflate **6**. It is conceivable that aromatization rapidly converts **6** into the intermediate **7**. It has been reported that aryl triflates appear to be extremely stable



Scheme 3. Suggested mechanism for the formation of **2q**.

and unreactive compounds in comparison to triflates **3** derived from amides **1** (see Scheme 1).[19] In contrast to compounds **3** which are easily converted into intermediates **4** (see Scheme 1), triflate **6** persists in the reaction medium until it attacks the 2-naphthol. Compared to **4** which is a hard electrophile, triflate **6** is a soft species which reacts with 2-naphthol via formation of a C–C bond to give **2q**.[20]

In conclusion, we have developed a new one-pot synthesis of *N*-arylimidates via reaction of 2-naphthol with activated secondary amides using Tf_2O and 2-ClPyr. With the exception of oxindole, reaction of which proceeds via C–C bond formation to give 1-(1*H*-indol-2-yl)naphthalene-2-ol (**2q**), the other amides investigated in this study afforded *N*-arylimidates via formation of a C–O bond.

Acknowledgment

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11. *Modified procedure for the preparation of naphthalen-2-yl N-4-methoxyphenylpivalimidate* (**2a**): A solution of amide **1a** (310 mg, 1.5 mmol, 1 equiv) and 2-ClPyr (169 μL, 1.8 mmol, 1.2 equiv) in CH_2Cl_2 (10 mL) was cooled to −78 °C with dry ice in acetone, and Tf_2O (277 μL, 1.65 mmol, 1.1 equiv) was added via syringe under an argon atmosphere. After 5 min, the reaction mixture was warmed to 0 °C and 2-naphthol (216 mg, 1.5 mmol, 1 equiv) was added. The mixture was allowed to warm to 25 °C and stirred for another 3 h. The progress of the reaction was monitored by TLC. After completion, aq. NaOH (10 mL, 0.1 M) was added in order to neutralize the acidic salts. The organic phase was separated, washed with brine (10 mL), and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the residue purified by column chromatography (silica gel, 10% EtOAc in hexane) to afford **2a** as a white solid (480 mg, 96%).
12. *Naphthalen-2-yl N-4-methoxyphenylpivalimidate* (**2a**): White crystals, mp: 64–65 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.47 (s, 9H), 3.57 (s, 3H), 6.55 (d, J = 8.3 Hz, 2H), 6.82 (d, J = 8.3 Hz, 2H), 7.02 (br d, J = 8.6 Hz, 1H), 7.10 (br s, 1H), 7.30–7.71 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.5, 39.7, 55.7, 114.0, 118.9, 121.4, 123.1, 124.7, 126.7, 127.3, 127.4, 128.0, 129.5, 130.1, 134.3, 139.6, 152.7 (C–O), 156.1 (C=N); IR (KBr) ν: 3252 (w), 3054 (w), 2969 (m), 1672 (s), 1503 (s), 1242 (s), 1080 (s) cm^{-1}; MS (EI) m/z: 333 (M^+, 8), 190 (100), 134 (87), 115 (12), 77 (7), 57 (22). Anal. Calcd for $C_{22}H_{23}NO_2$: C, 79.25; H, 6.95; N, 4.20. Found: C, 79.34; H, 6.89; N, 3.96.
13. No signal due to the OH group was evident in the IR and ^{1}H NMR spectra of **2a**. Compared to 2-[(phenylimino)methyl)]naphthalene-1-ol which displays the imine carbon at δ 172.3 in the ^{13}C NMR spectra,[21] the analogous carbon signal of **2a** appears at δ 156.1.[12] The internal hydrogen bonding between the OH and imine nitrogen in the former seems to be responsible for deshielding the C=N. Based on X-ray crystallography results obtained for 1-[(3,5-dichlorophenylimino)methyl)]naphthalen-2-ol, the presence of internal hydrogen bonding between the C=N nitrogen and OH was substantiated.[22] More importantly, the appearance of the most abundant ion (or base peak) at m/z 190 in the mass spectrum[12] of **2a** reveals that the parent ion had mainly undergone C–O fission, leading to nitrilium ion **5** (Scheme 1, R^1 = MeO–C_6H_4–, R^2 = $(CH_3)_3$C–). On the other hand, observation of a low abundant nitrilum ion similar to **5** in the mass spectrum of 1-[(2-aminophenylimino)methyl]naphthalen-2-ol indicated that C–C fission is not a dominant fragmentation pathway in this imine.[23]
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16. *Naphthalen-1-yl N-p-tolylpivalimidate* (**2n**): White crystals, mp: 59–60 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.51 (s, 9H), 2.05 (s, 3H), 6.68 (br s, 4H), 6.78 (s, 1H), 7.17 (t, J = 7.8, 1H), 7.39 (d, J = 7.8, 1H), 7.47–8.17 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.0, 28.7, 40.0, 112.5, 121.1, 122.2, 122.9, 123.2, 125.5, 125.8, 126.5, 128.0, 129.0, 132.6, 134.9, 144.5, 150.4 (C–O), 162.6 (C=N); IR (KBr) ν: 3056 (w), 2972 (m), 2868 (w), 1666 (s), 1463 (m), 1207 (s), 1077 (s) cm^{-1}; MS (EI) m/z: 317 (M^+, 12), 174 (100), 118 (93), 91 (19), 57 (16%). Anal. Calcd for $C_{22}H_{23}NO$: C, 83.24; H, 7.30; N, 4.41. Found: C, 83.27; H, 7.21; N, 4.28.
17. *4-tert-Butylphenyl N-p-tolylpivalimidate* (**2o**): White crystals, mp: 71–72 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25 (s, 9H), 1.42 (s, 9H), 2.17 (s, 3H), 6.56 (d, J = 8.2, 2H), 6.67 (br s, 2H), 6.80 (d, J = 7.4, 2H), 7.06 (br s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.1, 28.6, 31.8, 34.5, 39.5, 118.8, 121.4, 125.9, 128.9, 132.0, 144.3, 146.5, 152.8, 163.6; IR (KBr) ν: 2963 (m), 1668 (s), 1503 (s), 1214 (s), 1082 (s), 819 (s) cm^{-1}; MS (EI) m/z: 323 (M^+, 6), 174 (100), 118 (94), 91 (24), 57 (13%); Anal. Calcd for $C_{22}H_{29}NO$: C, 81.69; H, 9.04; N, 4.33. Found: C, 81.76; H, 9.37; N, 4.88.
18. *1-(1H-Indol-2-yl)naphthalen-2-ol* (**2q**): White crystals, mp: 171–172 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.15 (br s, 1H, OH), 6.82 (s, 1H), 7.27 (t, J = 7.9, 1H), 7.31 (m, 2H), 7.42 (m, 2H), 7.49 (d, J = 8.2, 1H), 7.72 (d, J = 8.2, 1H), 7.78 (d, J = 7.9, 1H), 7.88 (t, J = 8.9, 2H), 8.23 (br s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 105.0, 111.6, 112.3, 117.7, 121.0, 121.2, 123.3, 124.1, 124.7, 127.7, 128.7, 129.1, 129.3, 130.7, 131.4, 133.8, 137.5, 152.6; IR (KBr) ν: 3451 (s, OH), 3344 (s, NH), 3049 (w), 1589 (m), 1340 (s), 1199 (s) cm^{-1}; MS (EI) m/z: 259 (M^+, 100), 230 (28), 202 (12), 120 (8%); Anal. Calcd for $C_{18}H_{13}NO$: C, 83.37; H, 5.05; N, 5.40. Found: C, 83.41; H, 5.12; N, 5.44.
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