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Versatile and chemoselective transformation of aliphatic and aromatic secondary amides to nitriles

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ABSTRACT

Triflic anhydride in combination with 2-fluoropyridine effectively dehydrates secondary amides to afford nitriles under mild reaction conditions. The reaction is general in scope and compatible with the use of aliphatic, α,β-unsaturated, aromatic, and heteroaromatic amides bearing either secondary, tertiary, or benzylic *N*-alkyl groups. The reaction also shows good to excellent chemoselectivity for the secondary amide and tolerates several labile functional groups.

1. Introduction

Nitriles participate in a wide range of transformations and are thus versatile and powerful synthetic intermediates for organic synthesis. For example, the cyano group serves as a good leaving group to generate reactive species such as iminium ions, carbanions, and radicals.[1] It stabilizes α-carbanion and allows the syntheses of amines[1,2] and carbonyl compounds[3] via umpolung.[4] In addition, nucleophilic or radical addition to nitriles leads to several important classes of compounds including amines,[5] ketones,[6] and aldehydes.[7]

Nitriles are also widely present in natural products, bioactive compounds,[8–10] and materials.[11] For these reasons, many methods have been developed for the synthesis of nitriles,[12,13] most of which rely on cyanide addition or substitution reactions or dehydration of oximes[13b–f] and amides.[13d–u] Among the methods that have been developed for the dehydration of amides, reactions that employ secondary amides as substrates are rare.[13o–t] Nonetheless, the classical Von Braun amide degradation using PCl_5 is suitable for the dehydration of secondary and tertiary benzamides.[14] However, because of the vigorous conditions required, this reaction has rarely been used for the synthesis of nitriles. Gribble and Perni improved the protocol by using $POCl_3$ as the dehydration agent.[15] But the reaction requires *N*-*tert*-butylamides as the substrates. Recently, Prati and co-workers,[13s] further optimized the reaction conditions by using $(PhO)_3P$-halogen (Br_2 or Cl_2) combination as the dehydration agents. This method accommodates secondary and tertiary amides with a wide variety of *N*-substituents including benzyl, allyl, tertiary and even primary alkyl groups. Although significant progress has been achieved for the synthesis of nitriles from amides, most of the reported methods still suffer from limited substrate scope and/or harsh reaction conditions. In addition, the chemoselectivity of the dehydration reactions has rarely been addressed.[13t]

With our continued interest in developing synthetic methods employing readily available amides as the substrates,[16] we report herein a convenient method for the dehydration of secondary amides to give nitriles using triflic anhydride (Tf_2O)[17]/2-fluoropyridine (2-F-Py).[18]

2. Results and discussion

Our discovery of the nitrile synthesis stemmed from an attempt to cyclize secondary amide **1-1** using Tf_2O/2-F-Py (Scheme 1). The reaction led to the formation of nitrile **2-1** in 55% yield instead of the desired ketone **3**. A survey of the literature showed that only two reports have used Tf_2O to convert secondary amides to nitriles. Kunz and Pleuss demonstrated in one reaction that Tf_2O transforms quantitatively *N*-glycosyl *p*-methoxybenzamide to *p*-

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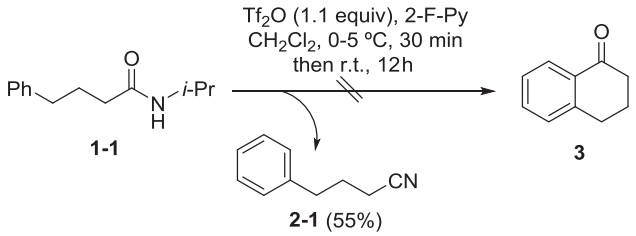
methoxybenzonitrile.[13q] However, no experimental procedure was provided and the protocol suffers from low atom economy. In their combinatorial synthesis of isoxazoles, Haino and Fukazawa employed a large excess of Tf_2O/pyridine to cleave a secondary amide linkage, leading to aryl nitriles.[13r] Thus, we decided to develop a mild and general method for the direct transformation of secondary amides to nitriles using Tf_2O as the dehydration agent.

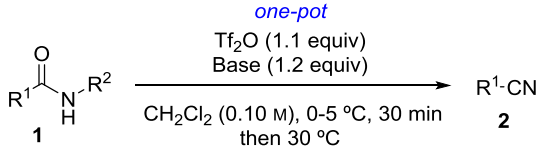


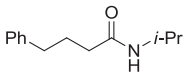
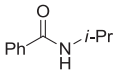
Scheme 1. Unexpected synthesis of nitrile **2-1** from secondary amide **1-1**.

We first examined the effect of base on the reaction of substrate **1-1** in CH_2Cl_2. The substrate was treated with Tf_2O and a base at 0 °C for 30 min and then at 30 °C until the complete consumption of the substrate (monitored with TLC). In the absence of a base, the desired nitrile was obtained in only 13% yield (Table 1, entry 1). Trialkyl amines such as Et_3N and *i*-Pr_2NEt were not effective. Various pyridine-derived bases were tested and 2-chloropyridine (2-Cl-Py, entry 7) and 2-fluoropyridine (2-F-Py, entry 8) gave the best yields. The effect of these two bases on the nitrile formation was thus further investigated using *N*-isopropylbenzamide (**1-7**) as the substrate. The results show that 2-F-Py (yield: 71%, entry 10) is superior to 2-Cl-Py (yield: 51%, entry 9) as a base for the Tf_2O-promoted dehydration reaction.

A survey of the effect of substrate concentration on the reaction showed that 0.2 M of amide in CH_2Cl_2 gave the best yield (83%). Thus, the optimum conditions for the dehydration of secondary amides to nitriles involve the use of 1.1 equiv of Tf_2O and 1.2 equiv of 2-F-Py with a substrate concentration of 0.2 M in CH_2Cl_2. The reagents were mixed at 0 °C and the reaction mixture was kept at the same temperature for 30 min, followed by at 30 °C until the disappearance of the substrate.

Table 1
Screening of the base additive

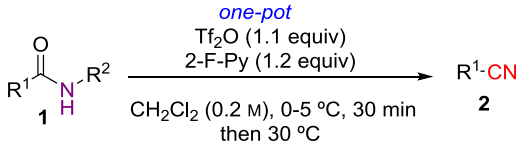


Entry	Amide	Base	**2** (% Yield)[a]
1		—	13
2		Et_3N	Trace
3		*i*-Pr_2NEt	Trace
4		Pyridine	8
5		2,6-Lutidine	Trace
6		DTBMP	44
7		2-Cl-Py	58
8		2-F-Py	55
9		2-Cl-Py	51
10		2-F-Py	71

[a] Isolated yield.

With the optimized reaction conditions defined, the scope of the reaction was investigated (Table 2). The dehydration reaction is compatible with the use of both aliphatic (entries 1–5, 73–85% yield) and aromatic amides (entries 7, 8, 11–14, 74–93% yield). Note that even hindered amide **1-5** reacted smoothly to give 1-adamantanecarbonitrile **2-5** in 73% yield. 2-Phenylacetamide **1-6** failed to afford the corresponding nitrile. The *N*-substituent has a dramatic effect on the reaction. Branched alkyl groups including isopropyl, cyclohexyl, cyclopentyl, *tert*-butyl or a benzyl group are well tolerated. In contrast, substrates bearing primary *N*-alkyl groups such as Me and *n*-Bu failed to form the desired nitriles (entries 9 and 10). For the naphthamides, both α- and β isomers reacted smoothly to give 1-naphthonitrile **2-13** and 2-naphthonitrile **2-14** in 93% and 85% yields, respectively. The chiral amide **1-15** also reacted without incident to give benzonitrile **2-15** in 74% yield. Finally, vinylogous benzamide derivative **1-16**[19m] is also a viable substrate and reacted chemoselectively to produce the α,β-unsaturated nitrile **2-16** in 66% yield.

Table 2
Tf_2O-Activated transformation of secondary amides to nitriles



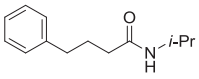
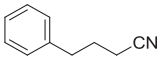
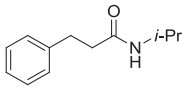
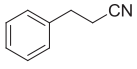
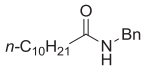
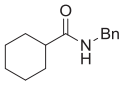
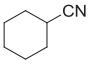
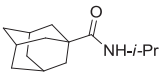
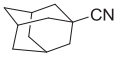
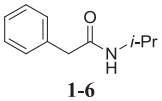
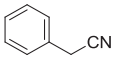
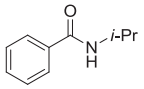
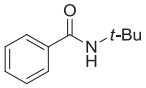
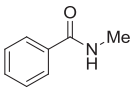
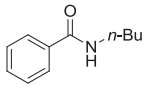
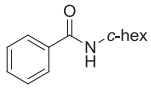
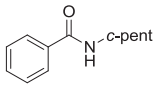
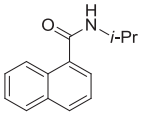
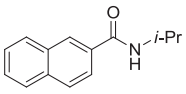
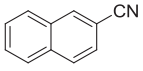
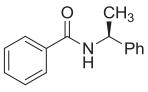
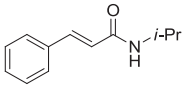
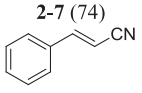
Entry	Substrate	Time (h)	Product (% yield)[a]
1	 **1-1**	12	 **2-1** (79)
2	 **1-2**	12	 **2-2** (76)
3	 **1-3**	7	n-$C_{10}H_{21}CN$ **2-3** (85)
4	 **1-4**	3	 **2-4** (78)
5	 **1-5**	12	 **2-5** (73)
6	 **1-6**	12	 **2-6** (trace)
7	 **1-7**	12	 **2-7** (83)
8	 **1-8**	3	 **2-7** (74)

Table 2 (*continued*)

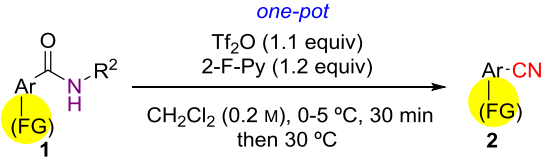
Entry	Substrate	Time (h)	Product (% yield)[a]
9	 **1-9**	16	 **2-7** (trace)
10	 **1-10**	16	 **2-7** (trace)
11	 **1-11**	12	 **2-7** (83)
12	 **1-12**	12	 **2-7** (82)
13	 **1-13**	7	 **2-13** (93)
14	 **1-14**	12	 **2-14** (85)
15	 **1-15**	3	 **2-7** (74)
16	 **1-16**	16	 **2-16** (66)

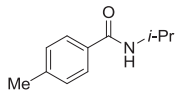
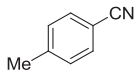
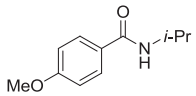
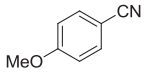
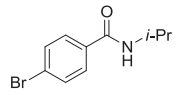
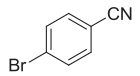
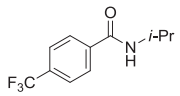
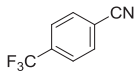
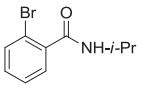
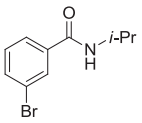
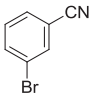
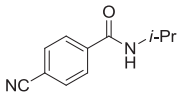
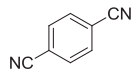
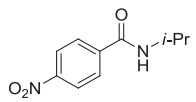
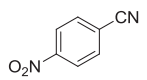
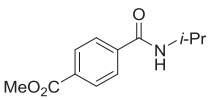
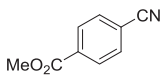
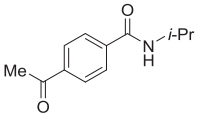
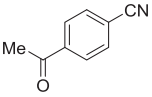
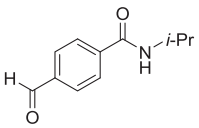
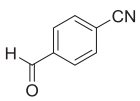
[a] Isolated yield.

We next turned our attention to the chemoselectivity of the reaction. Benzamides with diverse substituents on the aryl ring were first examined (Table 3). The dehydration reaction tolerated substituents having different electronic properties (entries 1–13). In general, substrates bearing electron-withdrawing groups outperform those with electron-donating groups. The position of the substituents does not affect the yields (entries 3, 5 and 6). The reaction proved tolerant of substrates bearing labile functional groups such as esters (entries 9 and 12), a ketone (entry 10), an aldehyde (entry 11), and an acetal group (entry 13), furnishing the corresponding nitriles in good to excellent yields. These entries highlight the usefulness of the current method for the synthesis of functionalized nitriles.

The reaction of heteroaromatic amides *N*-cyclohexylthiophene-2-carboxamide (entry 14) and *N*-isopropylbenzothiophenamide (entry 15) produced nitriles **2-30** and **2-31** in 73% and 87% yields, respectively. *N*-(*tert*-Butyl)-4-cyanobenzamide **1-32** reacted similarly as its *N*-*iso*-propyl homologous **1-23** to give nitrile **2-23** in 91% yield (entry 16). As can be seen from entry 17, the reaction can't distinguish between primary and secondary amides, both were converted to cyano groups. The reaction of carboxylic acid group-containing secondary amide **1-34** produced the desired product in 50% yield (entry 16).

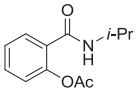
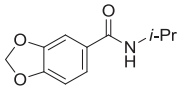
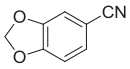
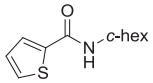
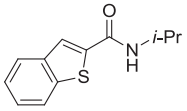
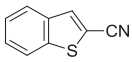
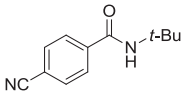
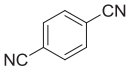
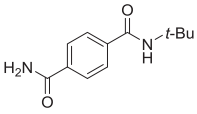
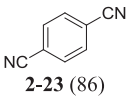
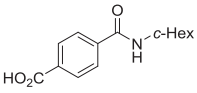
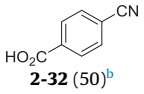
Table 3
Tf_2O-Activated transformation of secondary amides to nitriles



Entry	Substrate	Time (h)	Product (% yield)[a]
1	 **1-17**	12	 **2-17** (67)
2	 **1-18**	12	 **2-18** (65)
3	 **1-19**	12	 **2-19** (80)
4	 **1-20**	1	 **2-20** (75)
5	 **1-21**	12	 **2-21** (77)
6	 **1-22**	12	 **2-22** (81)
7	 **1-23**	1	 **2-23** (93)
8	 **1-24**	1	 **2-24** (95)
9	 **1-25**	6	 **2-25** (80)
10	 **1-26**	5	 **2-26** (79)
11	 **1-27**	4	 **2-27** (46)

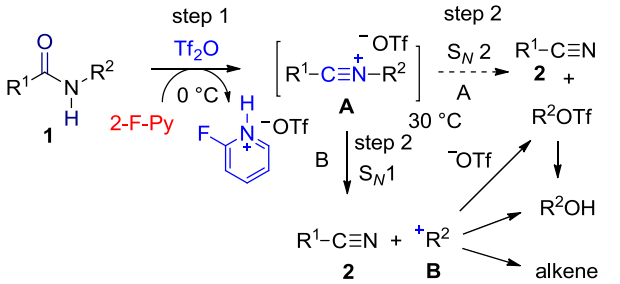
(*continued on next page*)

Table 3 (*continued*)

Entry	Substrate	Time (h)	Product (% yield)[a]
12	 **1-28**	3	 **2-28** (90)
13	 **1-29**	3	 **2-29** (89)
14	 **1-30**	7	 **2-30** (73)
15	 **1-31**	6	 **2-31** (87)
16	 **1-32**	3	 **2-23** (91)
17	 **1-33**	6	 **2-23** (86)
18	 **1-34**	6	 **2-32** (50)[b]

[a] Isolated yield.
[b] Tf_2O (2.2 equiv) and 2-F-Py (2.4 equiv).

A plausible mechanism for the nitrile formation is provided based on results in this work and those reported[13o–t,14,15] (Scheme 2). The key intermediate, the nitrilium ion **A**[16b,c,18] is generated upon treating the amide with Tf_2O and 2-F-Py. This reactive species loses the *N*-substituent R^2 to produce nitrile **2** via either an S_N2 (path A) or an S_N1 reaction (path B). The fact that the reaction performs well when R^2 is secondary, tertiary or benzyl substituents but not when R^2 equals primary substituents excludes the S_N2 mechanism. Primary carbocations are highly unstable and difficult to form. Thus substrates bearing a Me or an *n*-Bu group at the amidyl nitrogen failed to afford the desired nitrile. Hence, the nitrilium ion most likely decomposes through an S_N1 type mechanism (pathway B).



Scheme 2. Plausible mechanism for the Tf_2O mediated transformation of secondary amides to nitriles.

3. Conclusion

In summary, we have developed a versatile method for the direct transformation of secondary amides to nitriles under mild reaction conditions (30 °C for 1–16 h). The reaction tolerates both aliphatic and aromatic amides bearing secondary, tertiary, and benzylic *N*-alkyl groups. The reaction is remarkably chemoselective and a number of sensitive functional groups including esters, a ketone, and even an aldehyde remained intact during the transformation.

4. Experimental section

4.1. General methods

^1H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 (^1H/400 MHz, ^{13}C/100 MHz) spectrometer and a Bruker 500 (^1H/500 MHz, ^{13}C/125 MHz) spectrometer. Chemical shifts are expressed in parts per million (δ, ppm) relative to an internal standard of residual chloroform (7.26 ppm for ^1H NMR and 77.0 ppm for ^{13}C NMR). Data for ^1H NMR are reported as chemical shift (multiplicity, coupling constant, number of proton). GC–MS were recorded on a Shimadzu GCMS-QP2010 Plus. Melting points were determined on a Büchi M560 Automatic Melting Point apparatus. Infrared spectra were recorded with a Nicolet Avatar 330 FT-IR spectrometer using film or KBr pellet technique.

Silica gel (300–400 mesh) was used for flash column chromatography, eluting (unless otherwise stated) with ethyl acetate/petroleum ether (PE) (60–90 °C) mixture. Tf_2O was distilled over phosphorous pentoxide and used within a week. THF was distilled over sodium benzophenone ketyl under N_2. Dichloromethane was distilled over calcium hydride under N_2.

4.2. General procedure for the transformation of amides into nitriles

To an ice bath-cooled solution of a secondary amide (1.0 mmol) and 2-fluoropyridine (1.2 mmol) in anhydrous CH_2Cl_2 (5 mL) was added Tf_2O (1.1 mmol). After being stirred for 0.5 h, the reaction mixture was warmed to 30 °C and stirred until completion of the reaction (monitored by TLC analysis). The reaction was quenched with 1 M HCl (1.0 mL), and the mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with saturated sodium carbonate (5 mL) and brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with ethyl acetate/petroleum ether to afford the corresponding nitrile.

*4.2.1. 4-Phenylbutyronitrile (**2-1**).* Following the general procedure, the reaction of amide **1-1** (205 mg, 1.0 mmol) gave, after chromatographic separation eluting with EtOAc/PE (*v*/*v*=1:10), the known nitrile[19a] **2-1** (115 mg, yield: 79%) as a colorless oil; IR (film) ν_{max}: 3027, 2913, 2850, 2246 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.92–2.03 (m, 2H), 2.30 (t, *J*=7.1 Hz, 2H), 2.77 (t, *J*=7.5 Hz, 2H), 7.15–7.21 (m, 2H), 7.21–7.27 (m, 1H), 7.27–7.36 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 16.3, 26.8, 34.3, 119.4, 126.4, 128.4, 128.6, 139.6 ppm; MS (EI, *m*/*z*): 145 (40, M^+), 104 (28), 91(100), 65 (19); t_R (GC)=8.670 min.

*4.2.2. 3-Phenylpropanenitrile (**2-2**).* Following the general procedure, the reaction of amide **1-2** (191 mg, 1.0 mmol) gave, after chromatographic separation eluting with EtOAc/PE (*v*/*v*=1:10), the known nitrile[19b] **2-2** (100 mg, yield: 76%) as a colorless oil; IR (film) ν_{max}: 3029, 2916, 2849, 2246 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.59 (t, *J*=7.6 Hz, 2H), 2.94 (t, *J*=7.6 Hz, 2H), 7.15–7.42 (m,

5H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.2, 31.4, 119.1, 127.1, 128.2, 128.8, 138.0 ppm; MS (EI, *m*/*z*): 131 (28, M^+), 91 (100), 65 (15); t_R (GC)=7.948 min.

*4.2.3. Undecanenitrile (**2-3**).* Following the general procedure, the reaction of amide **1-3** (138 mg, 0.5 mmol) gave, after chromatographic separation eluting with EtOAc/PE (*v*/*v*=1:10), the known nitrile[19c] **2-3** (71 mg, yield: 85%) as a colorless oil; IR (film) ν_{max}: 2963, 2922, 2855, 2246 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.88 (t, *J*=7.0 Hz, 3H), 1.24–1.34 (m, 12H), 1.40–1.48 (m, 2H), 1.61–1.69 (m, 2H), 2.33 (t, *J*=7.3 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 14.0, 17.0, 22.6, 25.3, 28.6, 28.7, 29.2 (2C), 29.4, 31.8, 119.7 ppm; MS (EI, *m*/*z*): 152 (4, M^+-CH3), 138 (22), 124 (54), 110 (73), 96 (97), 82 (95), 57 (60), 43 (70), 41(100); t_R (GC)=10.404 min.

*4.2.4. Cyclohexanecarbonitrile (**2-4**).* Following the general procedure, the reaction of amide **1-4** (217 mg, 1.0 mmol) gave, after chromatographic separation eluting with EtOAc/PE (*v*/*v*=1:10), the known nitrile[13m] **2-4** (85 mg, yield: 78%) as a colorless oil; IR (film) ν_{max}: 2959, 2917, 2849, 2246 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.36–1.56 (m, 4H), 1.64–1.79 (m, 4H), 1.79–1.89 (m, 2H), 2.55–2,71 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 23.9, 25.1, 27.9, 29.4, 122.5 ppm; MS (EI, *m*/*z*): 109 (18, M^+), 108 (30), 94 (40), 81 (30), 56 (100), 54 (83), 41 (91), 27 (22); t_R (GC)= 6.515 min.

*4.2.5. 1-Adamantanecarbonitrile (**2-5**).* Following the general procedure, the reaction of amide **1-5** (221 mg, 1.0 mmol) gave, after chromatographic separation eluting with EtOAc/PE (*v*/*v*=1:10), the known nitrile[19b] **2-5** (118 mg, yield: 73%) as a pale yellow solid. Mp 189–191 °C (lit.[19b] 192–195 °C); IR (film) ν_{max}: 2914, 2850, 2235 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.70–1.78 (m, 6H), 1.91–1.96 (m, 1H), 1.98–2.10 (m, 8H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 27.1 (2C), 27.6, 30.1, 35.7 (2C), 36.3, 38.2, 39.9 (2C), 125.2 ppm; MS (EI, *m*/*z*): 161 (48, M^+), 146 (23), 134 (100), 119 (12), 104 (15), 93 (55), 69 (20); t_R (GC)=9.197 min.

*4.2.6. Benzonitrile (**2-7**).* Following the general procedure, the reaction of amide **1-7** (163 mg, 1.0 mmol) gave, after chromatographic separation eluting with EtOAc/PE (*v*/*v*=1:10), the known nitrile[13m] **2-7** (85 mg, yield: 83%) as a pale yellow oil; IR (film) ν_{max}: 3034, 2926, 2872, 2231 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.43–7.53 (m, 2H), 7.57–7.71 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 112.3, 118.7, 129.0, 132.1, 132.7 ppm; MS (EI, *m*/*z*): 103 (100, M^+), 76 (55), 50 (28), 28 (62); t_R (GC)=6.353 min.

*4.2.7. Benzonitrile (**2-7**).* Following the general procedure, the reaction of amide **1-8** (177 mg, 1.0 mmol) gave, after chromatographic separation eluting with EtOAc/PE (*v*/*v*=1:10), the known nitrile[13m] **2-7** (76 mg, yield: 74%) as a pale yellow oil; IR (film) ν_{max}: 3034, 2926, 2872, 2231 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.43–7.53 (m, 2H), 7.57–7.71 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 112.3, 118.7, 129.0, 132.1, 132.7 ppm; MS (EI, *m*/*z*): 103 (100, M^+), 76 (55), 50 (28), 28 (62); t_R (GC)=6.353 min.

*4.2.8. Benzonitrile (**2-7**).* Following the general procedure, the reaction of amide **1-11** (203 mg, 1.0 mmol) gave, after chromatographic separation eluting with EtOAc/PE (*v*/*v*=1:10), the known nitrile[13m] **2-7** (86 mg, yield: 83%) as a pale yellow oil; IR (film) ν_{max}: 3034, 2926, 2872, 2231 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.43–7.53 (m, 2H), 7.57–7.71 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 112.3, 118.7, 129.0, 132.1, 132.7 ppm; MS (EI, *m*/*z*): 103 (100, M^+), 76 (55), 50 (28), 28 (62); t_R (GC)=6.353 min.

*4.2.9. Benzonitrile (**2-7**).* Following the general procedure, the reaction of amide **1-12** (189 mg, 1.0 mmol) gave, after chromatographic separation eluting with EtOAc/PE (*v*/*v*=1:10), the known nitrile[13m] **2-7** (84 mg, yield: 82%) as a pale yellow oil; IR (film) ν_{max}: 3034, 2926, 2872, 2231 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.43–7.53 (m, 2H), 7.57–7.71 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 112.3, 118.7, 129.0, 132.1, 132.7 ppm; MS (EI, *m*/*z*): 103 (100, M^+), 76 (55), 50 (28), 28 (62); t_R (GC)=6.353 min.

*4.2.10. 1-Naphthonitrile (**2-13**).* Following the general procedure, the reaction of amide **1-13** (213 mg, 1.0 mmol) gave, after chromatographic separation eluting with EtOAc/PE (*v*/*v*=1:10), the known nitrile[19d] **2-13** (142 mg, yield: 93%) as a white solid. Mp 35–36 °C (lit.[19d] 35–36 °C); IR (film) ν_{max}: 3067, 2916, 2849, 2221 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.46–7.53 (m, 1H), 7.57–7.63 (m, 1H), 7.65–7.70 (m, 1H), 7.85–7.93 (m, 2H), 8.05 (d, *J*=8.5 Hz, 1H), 8.21 (d, *J*=8.5 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 110.1, 117.7, 124.8, 125.0, 127.5, 128.5, 128.6, 132.3, 132.5, 132.8, 133.2 ppm; MS (EI, *m*/*z*): 154 (12), 153 (100, M^+), 126 (24), 125 (9), 76 (10), 63 (13), 28 (20); t_R (GC)=11.517 min.

*4.2.11. 2-Naphthonitrile (**2-14**).* Following the general procedure, the reaction of amide **1-14** (213 mg, 1.0 mmol) gave, after chromatographic separation eluting with EtOAc/PE (*v*/*v*=1:10), the known nitrile[19e] **2-14** (130 mg, yield: 85%) as a white solid. Mp 65–67 °C (lit.[19f] 65–66 °C); IR (film) ν_{max}: 3059, 2917, 2852, 2225 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.56–7.66 (m, 3H), 7.86–7.96 (m, 3H), 8.17–8.25 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 109.4, 119.2, 126.3, 127.6, 128.0, 128.4, 129.0, 129.2, 132.2, 134.1, 134.6 ppm; MS (EI, *m*/*z*): 154 (12), 153 (100, M^+), 126 (28), 125 (9), 76 (9), 63 (10); t_R (GC)=9.703 min.

*4.2.12. Benzonitrile (**2-7**).* Following the general procedure, the reaction of amide **1-15** (225 mg, 1.0 mmol) gave, after chromatographic separation eluting with EtOAc/PE (*v*/*v*=1:10), the known nitrile[13m] **2-7** (76 mg, yield: 74%) as a pale yellow oil; IR (film) ν_{max}: 3034, 2926, 2872, 2231 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.43–7.53 (m, 2H), 7.57–7.71 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 112.3, 118.7, 129.0, 132.1, 132.7 ppm; MS (EI, *m*/*z*): 103 (100, M^+), 76 (55), 50 (28), 28 (62); t_R (GC)=6.353 min.

*4.2.13. Cinnamonitrile (**2-16**).* Following the general procedure, the reaction of amide **1-16** (189 mg, 1.0 mmol) gave, after chromatographic separation eluting with EtOAc/PE (*v*/*v*=1:10), the known nitrile[19g] **2-17** (85 mg, yield: 66%) as a pale yellow wax; IR (film) ν_{max}: 3053, 2917, 2849, 2217 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.87 (d, *J*=16.7 Hz, 1H), 7.37–7.46 (m, 6H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 96.3, 118.1, 127.3, 129.0, 131.1, 133.5, 150.5 ppm; MS (EI, *m*/*z*): 130 (10), 129 (100, M^+), 128 (26), 102 (46), 76 (15), 63 (8), 51 (20); t_R (GC)=9.584 min.

*4.2.14. p-Toluonitrile (**2-17**).* Following the general procedure, the reaction of amide **1-17** (177 mg, 1.0 mmol) gave, after chromatographic separation eluting with EtOAc/PE (*v*/*v*=1:10), the known nitrile[19h] **2-17** (78 mg, yield: 67%) as a white solid. Mp 27–28 °C; IR (film) ν_{max}: 3019, 2959, 2911, 2850, 2226 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.42 (s, 3H), 7.22–7.30 (m, 2H), 7.46–7.60 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.8, 109.3, 119.1, 129.8, 132.0, 143.6 ppm; MS (EI, *m*/*z*): 118 (9), 117(100, M^+), 116 (61), 90 (47), 89 (27), 63 (13), 51 (6), 39 (10); t_R (GC)=7.599 min.

*4.2.15. Anisonitrile (**2-18**).* Following the general procedure, the reaction of amide **1-18** (193 mg, 1.0 mmol) gave, after chromatographic separation eluting with EtOAc/PE (*v*/*v*=1:10), the known nitrile[13m] **2-18** (86 mg, yield: 65%) as a white solid. Mp 56–58 °C (lit.[19g] 55–57 °C); IR (film) ν_{max}: 3005, 2916, 2849, 2224 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.86 (s, 3H), 6.91–7.00 (m, 2H), 7.54–7.64 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 55.5, 104.0, 114.7, 119.2,

133.9, 162.8 ppm; MS (EI, *m*/*z*): 134 (9), 133 (100, M^+), 118 (10), 103 (47), 90 (50), 76 (12), 63 (18); t_R (GC)=8.148 min.

*4.2.16. 4-Bromobenzonitrile (**2-19**).* Following the general procedure, the reaction of amide **1-19** (121 mg, 0.5 mmol) gave, after chromatographic separation eluting with EtOAc/PE (*v*/*v*=1:10), the known nitrile[19i] **2-19** (73 mg, yield: 80%) as a white solid. Mp 109–111 °C (lit.[19b] 114–115 °C); IR (film) ν_{max}: 3089, 2917, 2849, 2224 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.49–7.56 (m, 2H), 7.58–7.67 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 111.2, 117.9, 127.9, 132.5, 133.3 ppm; MS (EI, *m*/*z*): 183 (50), 181 (53, M^+), 102 (100), 75 (40), 50 (20); t_R (GC)=7.139 min.

*4.2.17. 4-Trifluormethylbenzonitrile (**2-20**).* Following the general procedure, the reaction of amide **1-20** (231 mg, 1.0 mmol) gave, after chromatographic separation eluting with EtOAc/PE (*v*/*v*=1:10), the known nitrile[19h] **2-20** (127 mg, yield: 75%) as a white solid. Mp 36–38 °C; IR (film) ν_{max}: 3067, 2955, 2918, 2849, 2237 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.76 (d, *J*=8.2 Hz, 2H), 7.81 (d, *J*=8.2 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 116.1, 117.4, 123.0 (d, *J*=272.8 Hz), 126.2 (q, *J*=3.7 Hz), 132.7, 134.5 (d, *J*=34.0 Hz) ppm; MS (EI, *m*/*z*): 172 (8), 171 (100, M^+), 170 (25), 152 (56), 121 (78), 102 (13), 75 (21), 69 (7), 50 (11); t_R (GC)=5.923 min.

*4.2.18. 2-Bromobenzonitrile (**2-21**).* Following the general procedure, the reaction of amide **1-21** (121 mg, 0.5 mmol) gave, after chromatographic separation eluting with EtOAc/PE (*v*/*v*=1:10), the known nitrile[19a] **2-21** (70 mg, yield: 77%) as a white solid. Mp 53–55 °C; IR (film) ν_{max}: 3092, 2917, 2830, 2225 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.36–7.52 (m, 2H), 7.59–7.73 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 115.8, 117.0, 125.2, 127.6, 133.1, 133.8, 134.2 ppm; MS (EI, *m*/*z*): 183 (67), 181 (70, M^+), 102 (100), 75 (30), 50 (19); t_R (GC)=9.353 min.

*4.2.19. 3-Bromobenzonitrile (**2-22**).* Following the general procedure, the reaction of amide **1-22** (121 mg, 0.5 mmol) gave, after chromatographic separation eluting with EtOAc/PE (*v*/*v*=1:10), the known nitrile[19h] **2-22** (74 mg, yield: 81%) as a pale yellow solid. Mp 35–36 °C; IR (film) ν_{max}: 3071, 2917, 2849, 2232 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.33–7.40 (m, 1H), 7.55–7.65 (m, 1H), 7.65–7.85 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 114.1, 117.1, 122.8, 130.5, 130.6, 134.6, 136.0 ppm; MS (EI, *m*/*z*): 183 (57), 181 (60, M^+), 102 (100), 75 (30), 50 (19); t_R (GC)=7.768 min.

*4.2.20. Terephthalonitrile (**2-23**).* Following the general procedure, the reaction of amide **1-23** (188 mg, 1.0 mmol) gave, after chromatographic separation eluting with EtOAc/PE (*v*/*v*=1:10), the known nitrile[19g] **2-23** (119 mg, yield: 93%) as a white solid. Mp 226–228 °C (lit.[19g] 226–228 °C); IR (film) ν_{max}: 3098, 3054, 2917, 2851, 2231, 1503, 1277 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.80 (s, 4H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 116.7, 116.9, 132.8 ppm; MS (EI, *m*/*z*): 128 (100, M^+), 101 (30), 75 (14), 50 (16); t_R (GC)=8.056 min.

*4.2.21. 4-Nitrobenzonitrile (**2-24**).* Following the general procedure, the reaction of amide **1-24** (208 mg, 1.0 mmol) gave, after chromatographic separation eluting with EtOAc/PE (*v*/*v*=1:10), the known nitrile[13m] **2-24** (141 mg, yield: 95%) as a pale yellow solid. Mp 147–149 °C (lit.[13m] 148–149 °C); IR (film) ν_{max}: 3100, 3054, 2913, 2854, 2233 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.90 (d, *J*=8.4 Hz, 2H), 8.37 (d, *J*=8.4 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 116.7, 118.3, 124.2, 133.4, 150.2 ppm; MS (EI, *m*/*z*): 148 (53, M^+), 118 (12), 102 (100), 90 (32), 75 (51), 51 (31), 30 (50); t_R (GC)=10.106 min.

*4.2.22. Methyl 4-cyanobenzoate (**2-25**).* Following the general procedure, the reaction of amide **1-25** (111 mg, 0.5 mmol) gave, after chromatographic separation eluting with EtOAc/PE (*v*/*v*=1:10), the known nitrile[19f] **2-25** (65 mg, yield: 80%) as a white solid. Mp 66–68 °C (lit.19f 65–66 °C); IR (film) ν_{max}: 3079, 2957, 2922, 2851, 2229, 1719 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 3.94–3.99 (m, 3H), 7.70–7.88 (m, 2H), 8.01–8.24 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 52.6, 116.3, 117.8, 130.0, 132.1, 133.8, 165.3 ppm; MS (EI, *m*/*z*): 161 (28, M^+), 130 (100), 102 (50), 75 (16), 51 (9); t_R (GC)=10.209 min.

*4.2.23. 4-Acetylbenzonitrile (**2-26**).* Following the general procedure, the reaction of amide **1-26** (205 mg, 1.0 mmol) gave, after chromatographic separation eluting with EtOAc/PE (*v*/*v*=1:10), the known nitrile[19g] **2-26** (115 mg, yield: 79%) as a white solid. Mp 54–56 °C (lit.[19g] 56–58 °C); IR (film) ν_{max}: 3096, 2918, 2849, 2229, 1694 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 2.66 (s, 3H), 7.29 (d, *J*=8.4 Hz, 2H), 8.05 (d, *J*=8.4 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 26.6, 116.3, 117.8, 128.6, 132.4, 139.8, 196.4 ppm; MS (EI, *m*/*z*): 145 (22, M^+), 130 (100), 102 (55), 75 (17), 43 (12); t_R (GC)=8.703 min.

*4.2.24. 4-Formylbenzonitrile (**2-27**).* Following the general procedure, the reaction of amide **1-27** (191 mg, 1.0 mmol) gave, after chromatographic separation eluting with EtOAc/PE (*v*/*v*=1:10), the known nitrile[19j] **2-27** (61 mg, yield: 46%) as a white solid. Mp 103–105 °C (lit.[19j] 97–100 °C); IR (film) ν_{max}: 3094, 2917, 2849, 2229, 1706 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.83–7.87 (m, 2H), 7.98–8.02 (m, 2H), 10.1 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 117.6, 129.8, 132.8, 132.9, 138.8, 190.5 ppm; MS (EI, *m*/*z*): 131 (72, M^+), 130 (100), 102 (60), 75 (33), 50 (27); t_R (GC)=9.073 min.

*4.2.25. 2-Acetoxybenzonitrile (**2-28**).* Following the general procedure, the reaction of amide **1-28** (221 mg, 1.0 mmol) gave, after chromatographic separation eluting with EtOAc/PE (*v*/*v*=1:10), the known nitrile[19h] **2-28** (145 mg, yield: 90%) as a colorless oil; IR (film) ν_{max}: 3083, 2917, 2849, 2233, 1769 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 2.38 (s, 3H), 7.25–7.29 (m, 1H), 7.30–7.35 (m, 1H), 7.59–7.64 (m, 1H), 7.64–7.70 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 20.6, 107.0, 115.0, 123.1, 126.2, 133.1, 133.9, 152.2, 168.1 ppm; MS (EI, *m*/*z*): 161 (19, M^+), 119 (44), 91 (23), 43 (100); t_R (GC)=8.306 min.

*4.2.26. Piperonylonitrile (**2-29**).* Following the general procedure, the reaction of amide **1-29** (128 mg, 0.5 mmol) gave, after chromatographic separation eluting with EtOAc/PE (*v*/*v*=1:10), the known nitrile[19k] **2-29** (66 mg, yield: 89%) as a white solid. Mp 92–94 °C (lit.[19k] 90–92 °C); IR (film) ν_{max}: 3079, 2930, 2851, 2223 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 6.07 (s, 2H), 6.86 (d, *J*=8.0 Hz, 1H), 7.02 (s, 1H), 7.21 (d, *J*=8.0 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 102.1, 104.9, 109.0, 111.3, 118.8, 128.1, 148.0, 151.5 ppm; MS (EI, *m*/*z*): 147 (68, M^+), 146 (100), 62 (20), 38 (9); t_R (GC)=8.740 min.

*4.2.27. 2-Thiophenecarbonitrile (**2-30**).* Following the general procedure, the reaction of amide **1-30** (209 mg, 0.5 mmol) gave, after chromatographic separation eluting with EtOAc/PE (*v*/*v*=1:10), the known nitrile[13m] **2-30** (80 mg, yield: 73%) as a colorless oil; IR (film) ν_{max}: 3098, 2918, 2850, 2222 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.11–7.21 (m, 1H), 7.54–7.76 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 109.8, 114.1, 127.6, 132.5, 137.3 ppm; MS (EI, *m*/*z*): 110 (7), 109 (100, M^+), 58 (39), 45 (29), 39 (8); t_R (GC)=6.306 min.

*4.2.28. Benzothiophene-2-carbonitrile (**2-31**).* Following the general procedure, the reaction of amide **1-31** (219 mg, 1.0 mmol) gave, after chromatographic separation eluting with EtOAc/PE (*v*/*v*=1:10), the known nitrile[19i] **2-31** (139 mg, yield: 87%) as a pale yellow wax; IR (film) ν_{max}: 3090, 3058, 2962, 2850, 2216 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.44–7.57 (m, 2H), 7.80–7.95 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 109.7, 114.4, 122.4, 125.3,

125.7, 127.8, 134.9, 137.4, 141.3 ppm; MS (EI, *m*/*z*): 159 (100, M^+), 132 (8), 115 (7), 69 (8); t_R (GC)=9.539 min.

*4.2.29. Terephthalonitrile (**2-23**).* Following the general procedure, the reaction of amide **1-32** (202 mg, 1.0 mmol) gave, after chromatographic separation eluting with EtOAc/PE (*v*/*v*=1:10), the known nitrile[19g] **2-23** (116 mg, yield: 91%) as a white solid. Mp 226–228 °C (lit.[19g] 226–228 °C); IR (film) ν_{max}: 3098, 3054, 2917, 2851, 2231, 1503, 1277 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.80 (s, 4H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 116.7, 116.9, 132.8 ppm; MS (EI, *m*/*z*): 128 (100, M^+), 101 (30), 75 (14), 50 (16); t_R (GC)=8.056 min.

*4.2.30. Terephthalonitrile (**2-23**).* The reaction of amide **1-33** (67 mg, 0.3 mmol) also gave **2-23** (33 mg, yield: 86%).

*4.2.31. 4-Cyanobenzoic acid (**2-32**) (CAS: 619-65-8).* Following the general procedure, the reaction of amide **1-34** (124 mg, 0.5 mmol) gave, after chromatographic separation eluting with EtOAc/PE (*v*/*v*=2:1), the commercially available nitrile[19l] **2-32** (24 mg, yield: 32%) as a white solid. Mp 219–221 °C (lit.[19g] 219–221 °C); IR (film) ν_{max}: 3150, 3058, 2954, 2855, 2231, 1703 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 7.94–8.01 (m, 2H), 8.05–8.11 (m, 2H), 13.54 (br s, 1H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 115.5, 118.6, 130.4, 133.1, 135.3, 166.5 ppm; MS (EI, *m*/*z*): 147 (63, M^+), 131 (10), 130 (100), 119 (5), 102 (49), 76 (25), 75 (23); t_R (GC)=11.773 min.

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