Conjugate Addition – S_NAr Domino Reaction for the Synthesis of Benzo- or Pyridyl-Fused Lactams and Sultams

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Received 30 July 2010; revised 21 September 2010

Abstract: A versatile domino reaction that can be used for the synthesis of bicyclic benzo- or pyridyl-fused lactam and sultam derivatives is presented, enabling rapid synthesis of a variety of complex structures.

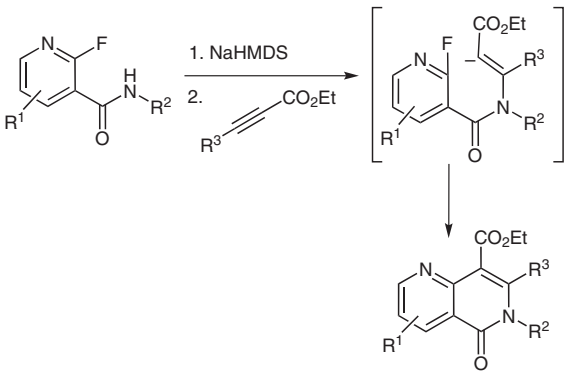
Key words: bicyclic compounds, domino reactions, heterocycles, Michael addition, nucleophilic aromatic substitution

The domino reaction methodology in organic synthesis has, in recent years, evolved into an efficient tool for making, for example, heterocyclic structures, and has allowed a rapid increase in molecular complexity, potentially leading to more efficient and environmentally benign synthetic processes.[1]

Derivatives of benzo- and pyridyl-fused lactams and sultams span several important classes of bicyclic heterocycles. The isoquinolinone and naphthyridinone skeletons have been found in naturally occurring alkaloids[2] such as dorianine[3] and ruprechstyril,[4] and a variety of biological and medicinal activities have been reported, such as NK_3 receptor antagonism[5] and topoisomerase I inhibition.[6] Benzo-fused sultams also show diverse biological activities, and a number of nonsteroidal anti-inflammatory agents (NSAIDs) based on the benzo-fused sultam skeleton, are commercially available, such as Meloxicam,[7] Ampiroxicam,[8] and Piroxicam.[9]

Several approaches to the synthesis of isoquinolinone and naphthyridinone derivatives have been reported, such as condensation reactions,[10] Baylis–Hillman reactions,[11] nitrogen substitution of isocoumarins,[12] aromatic substitutions,[13] and a number of transition-metal-based catalytic reactions.[14] Synthesis of benzo- and pyridyl-fused sultams have not received the same attention, although some synthetic approaches have been reported, such as ring expansion of benzoisothiazoles,[15] intramolecular free radical substitutions,[16] and organometallic cyclization reactions.[17]

The broad applicability of these bicyclic structures justifies continuing research into new approaches to their synthesis. We envisioned, and describe here, a method based on a conjugate addition – nucleophilic aromatic substitution domino reaction (Scheme 1).



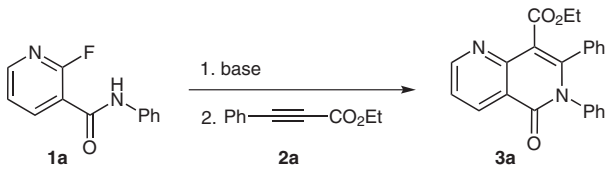
Scheme 1 Proposed reaction mechanism

We hypothesized that a deprotonated amide would add to a conjugate addition acceptor, creating an enolate intermediate, which would subsequently add to the aromatic moiety in a nucleophilic aromatic substitution reaction.

2-Fluoro-*N*-phenylnicotinamide (**1a**) and ethyl 3-phenylpropiolate (**2a**) were used as model substrates in an initial optimization study (Table 1). The reaction was carried out by deprotonation of the amide at room temperature, followed by addition of the alkyne and heating. Reaction temperature and time were the first parameters optimized (entries 1–6). Formation of the sterically crowded product required high temperatures; however, full conversion of the amide was obtained within hours at temperatures at or above 200 °C using microwave irradiation. Screening of different solvents showed that the polar aprotic solvents *N*,*N*-dimethylformamide (DMF) and *N*-methyl-2-pyrrolidinone (NMP) gave better results for this reaction (entries 4 and 7–9). Different hexamethyldisilazane (HMDS) bases were screened, and the results showed that use of NaHMDS increased the yield slightly (entries 10–12). Employing a larger excess of base (4 equiv) led to complex mixtures of side products and none of the desired product was formed (entries 13 and 14). Full conversion of the amide was obtained when 2.0 equivalents of alkyne was used (entries 10 and 15–18). The excess was required because the predominant side products of the reaction resulted from oligomerization of the conjugate addition intermediates prior to the ring-closing nucleophilic aromatic substitution. In these cases, the subsequent lack

SYNTHESIS 2010, No. 24, pp 4273–4281
Advanced online publication: 14.10.2010
DOI: 10.1055/s-0030-1258302; Art ID: T15710SS

Table 1 Optimization of Reaction Conditions



Entry	Solvent	Base (equiv)	Alkyne (equiv)	Temp (°C)[a]	Time (h)	Yield (%)[b]
1	NMP	NaH (1.2)	2.0	150	0.5	24
2	NMP	NaH (1.2)	2.0	150	4.0	45
3	NMP	NaH (1.2)	2.0	200	0.5	53
4	NMP	NaH (1.2)	2.0	200	4.0	81
5	NMP	NaH (1.2)	2.0	225	0.5	81
6	NMP	NaH (1.2)	2.0	250	0.5	85
7	toluene	NaH (1.2)	2.0	200	4.0	8
8	THF	NaH (1.2)	2.0	200	4.0	67
9	DMF	NaH (1.2)	2.0	200	4.0	88
10	DMF	NaHMDS (1.2)	2.0	200	4.0	90
11	DMF	KHMDS (1.2)	2.0	200	4.0	81
12	DMF	LiHMDS (1.2)	2.0	200	4.0	85
13	DMF	NaH (4.0)	2.0	200	4.0	0
14	DMF	NaHMDS (4.0)	2.0	200	4.0	0
15	DMF	NaHMDS (1.2)	1.0	200	4.0	50
16	DMF	NaHMDS (1.2)	1.2	200	4.0	55
17	DMF	NaHMDS (1.2)	1.5	200	4.0	65
18	DMF	NaHMDS (1.2)	4.0	200	4.0	88

[a] The reaction was heated by microwave irradiation.
[b] The reaction was evaluated using LC/MS analysis before workup. The product yield was determined by comparing the peak area to an internal standard solution using authentic samples as reference.

of alkyne led to incomplete amide conversion or to dimerization of the amide substrates.

Having obtained a set of optimal conditions, we then explored the scope of the reaction, starting with various amide substrates (Table 2).

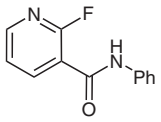
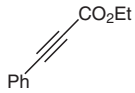
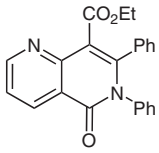
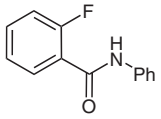
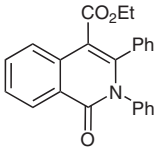
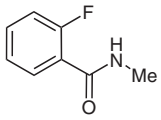
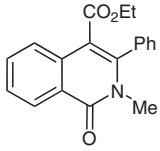
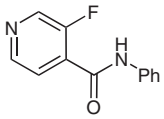
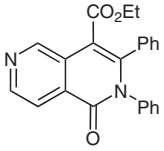
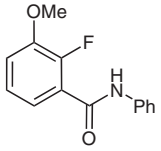
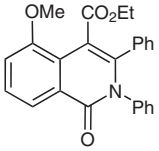
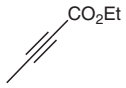
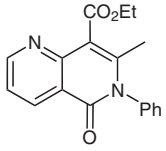
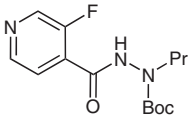
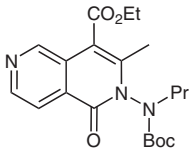
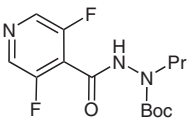
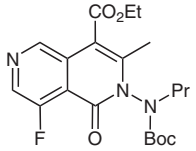
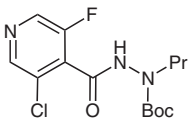
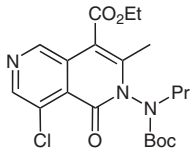
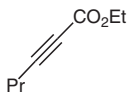
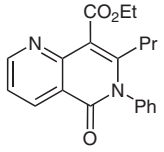
The range of aromatic rings tolerated by the reaction was found to extend from simple 2-fluoro-benzene (**1b**) to more activated fluoropyridines **1a** and **1d**, as well as to less activated 3-methoxy-2-fluorobenzene (**1e**), in yields ranging from 40 to 65% (Table 2, entries 1, 2, 4, and 5). Variation of the alkyne substituent (R^3) revealed a notable influence on the reaction outcome. Simple electron-donating alkyl and aryl groups were tolerated (entries 1, 6, and 10). However, electron-withdrawing groups, which activate the alkyne more towards conjugate addition, led to extensive oligomerization of the intermediate, instead of the ring-closing step. Additionally, attempts were made using the terminal alkyne ethyl propriolate and the TMS-protected analogue, ethyl 3-(trimethylsilyl)propiolate; however, in both cases, oligomerization was the predominant outcome. A modified reaction method (method B), involving slow addition of a dilute solution of the alkyne to a pre-heated, deprotonated amide solution, improved yields in some cases (entry 6). However, temperatures were restricted to 150 °C because higher temperatures led to dimerization of the amide substrates. Both simple alkyl and aryl groups, **1b** and **1c**, were tolerated as the amide N-substituent (R^2) (entries 2 and 3). Furthermore, a Boc-protected hydrazide moiety (**1f**,**g**,**h**) was also tolerated; however, these substrates led to lower yields because reaction temperatures were restricted to 100 °C, due to decomposition of the Boc group at higher temperatures (entries 7–9). Surprisingly, double halogenation of the aromatic ring led to extensive oligomerization, despite further activation of the nucleophilic aromatic substitution step. Increased steric interactions could explanation this observation, particularly at these lower temperatures.

Sulfonamides were also investigated as substrates for the domino reaction and showed similar reactivity, albeit with notable differences (Table 3). A more facile ring-closing step was expected, given the more electron-withdrawing properties of the sulfonamide group. Indeed, shorter reaction times and very little oligomerization of the intermediate were observed, resulting in better yields without the need for slow alkyne addition (compare Table 2, entry 6 and Table 3, entry 1). Surprisingly, a domino reaction was achieved when employing an alkyne with two electron-withdrawing groups, **2d** (Table 3, entry 5). However, steric interactions between the amide N-substituent and the alkyne substituent seemed to play a bigger role, impeding the domino reaction when both were bulky phenyl groups. When either of the phenyl groups was replaced by a smaller methyl group the domino reaction could proceed (Table 3, entries 1 and 4).

Unsuccessful attempts were made with both amides and sulfonamides to utilize activated olefins as the conjugate acceptors. No conjugate addition of the amides were observed despite heating to 250 °C using microwave irradiation and adding various Lewis acid catalysts. Intermediate analogues, **6a** and **6b**, were synthesized and subjected to the optimized reaction conditions, resulting in complete retro-conjugate addition at room temperature within minutes (Scheme 2). This indicates that the retro addition is faster than the ring-closing step.

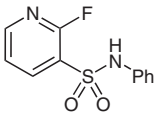
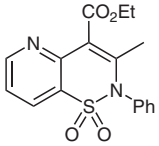
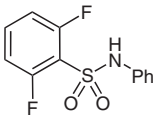
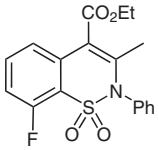
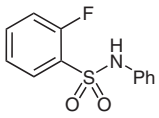
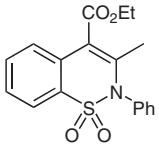
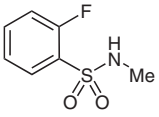
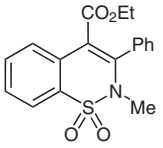
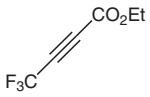
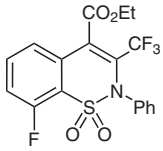
To extend the range of target structures, the domino reaction product **3b** was hydrolyzed and decarboxylated to yield 2,3-diphenyl-2*H*-isoquinolin-1-one (**9**; Scheme 3). Complete hydrolysis was achieved in a mixture of methanol and aqueous sodium hydroxide at room temperature within hours. The carboxylic acid was subsequently decarboxylated using microwave-assisted copper-catalyzed protodecarboxylation in a yield of 89%.[18]

Table 2 Reaction Scope with Amides

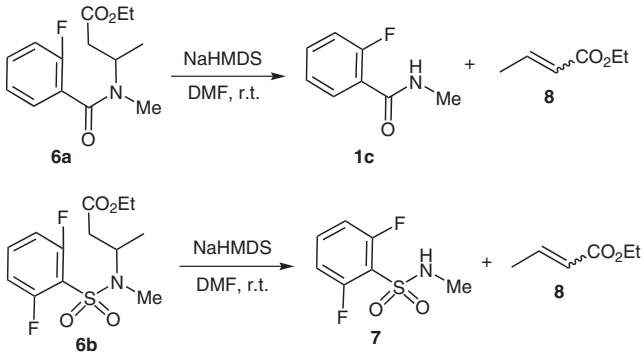
Entry	Amide	Alkyne	Product	Method[a]	Temp (°C)	Time (h)	Yield (%)[b]
1	**1a** 	**2a** 	**3a** 	A	200	4	65
2	**1b** 	**2a**	**3b** 	A	200	4	61
3	**1c** 	**2a**	**3c** 	A	200	4	52
4	**1d** 	**2a**	**3d** 	A	200	4	40
5	**1e** 	**2a**	**3e** 	A	200	4	63
6	**1a**	**2b** 	**3f** 	A B	200 150	4 16	36 48
7	**1f** 	**2b**	**3g** 	B	100	16	41
8	**1g** 	**2b**	**3h** 	B	100	16	24
9	**1h** 	**2b**	**3i** 	B	100	16	18
10	**1a**	**2c** 	**3j** 	A	200	4	53

[a] Method A: Alkyne addition at r.t., and heating using microwave irradiation. Method B: Slow alkyne addition at the reported temperatures.
[b] Yield of isolated product.

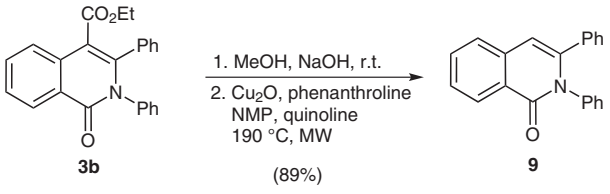
Table 3 Reaction Scope with Sulfonamides

Entry	Amide	Alkyne	Product	Method[a]	Temp (°C)	Time (h)	Yield (%)[b]
1	**4a** 	**2b**	**5a** 	A	200	1	64
2	**4b** 	**2b**	**5b** 	A	200	1	75
3	**4c** 	**2b**	**5c** 	B	150	16	38
4	**4d** 	**2a**	**5d** 	A	200	4	46
5	**4b**	**2d** 	**5e** 	B	150	16	36[c]

[a] Method A: Alkyne addition at r.t., and heating using microwave irradiation. Method B: Slow alkyne addition at the reported temperatures.
[b] Yield of isolated product.
[c] Regioselectivity of the conjugate addition was established using NOESY and ROESY spectroscopic analysis.



Scheme 2 Retro-conjugate addition



Scheme 3 Decarboxylation of **3b**

In conclusion, a versatile domino reaction has been developed for the synthesis of bicyclic benzo- or pyridyl-fused lactam and sultam derivatives. Additionally, the scope of the target structures has been extended by decarboxylation of the domino reaction products.

Oven-dried glassware was used when the reactions were performed under argon atmosphere. DMF, NMP and THF were dried using molecular sieves. NaHMDS, LiHMDS and KHMDS were titrated against 2,6-di-*tert*-butyl-4-methylphenol with fluorine as indicator. A solution of L-tryptophan in DMF was used as the internal standard in the optimization study. All reagents were obtained from commercial sources and used as received. ^{1}H and ^{13}C NMR spectra were recorded at either 500 MHz (^{1}H) and 126 MHz (^{13}C), or 600 MHz (^{1}H) and 151 MHz (^{13}C). The solvent ($CDCl_3$, DMSO, or CD_3OD) was used as internal reference. Chemical shifts (δ) and coupling constants (*J*) are expressed in ppm and Hertz respectively. High-resolution mass spectrometry (HRMS) was conducted with a MicroTOF mass spectrometer. Microwave-assisted reactions were performed with a Biotage Initiator 60 instrument.

2-Fluoro-*N*-phenylnicotinamide (1a)

Aniline (1.5 mL, 16 mmol) was added to 2-fluoronicotinic acid (2.15 g, 15.2 mmol), *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (2.91 g, 15.3 mmol) and 1-hydroxybenzotriazole (2.14 g, 15.8 mmol) in THF (60 mL). The reaction was stirred at r.t. for 16 h, then the reaction mixture was poured into H_2O (50 mL), extracted with EtOAc (3 × 50 mL), washed with sat. aq $NaHCO_3$ (3 × 50 mL) and brine (3 × 50 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (heptane–EtOAc) to obtain 2-fluoro-*N*-phenylnicotinamide (**1a**). Yield: 2.93 g (89%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.67 (ddd, *J* = 9.8, 7.5, 2.0 Hz, 1 H), 8.54 (d, *J* = 13.6 Hz, 1 H), 8.44–8.34 (m, 1 H), 7.66–7.63 (m, 2 H), 7.43 (ddd, *J* = 7.4, 4.8, 2.4 Hz, 1 H), 7.42–7.38 (m, 2 H), 7.20 (ddd, *J* = 8.5, 2.1, 1.0 Hz, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 159.7 (d, *J* = 234 Hz), 159.6, 150.7, 143.8, 137.2, 129.2, 125.3, 122.8, 120.7, 116.4 (d, *J* = 27 Hz).

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{10}FN_2O$: 217.0779; found: 217.0772.

2-Fluoro-*N*-phenylbenzamide (1b)
Synthesized as for **1a** using 2-fluorobenzoic acid and aniline. Yield: 86%.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.56–8.31 (m, 1 H), 8.19 (td, *J* = 8.0, 1.8 Hz, 1 H), 7.67 (d, *J* = 7.6 Hz, 2 H), 7.53 (dddd, *J* = 8.3, 7.2, 5.3, 1.9 Hz, 1 H), 7.42–7.36 (m, 2 H), 7.35–7.29 (m, 1 H), 7.18 (dddd, *J* = 9.5, 5.1, 2.2, 1.0 Hz, 2 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 161.2, 160.4 (d, *J* = 246 Hz), 137.7, 133.8, 132.4, 129.1, 125.1, 124.8, 120.6, 116.2 (d, *J* = 25.1 Hz).

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{11}FNO$: 216.0822; found: 216.0819.

2-Fluoro-*N*-methylbenzamide (1c)
Two drops of DMF were added to 2-fluorobenzoic acid (4.83 g, 32.7 mmol) and oxalyl chloride (10.0 mL, 118 mmol) in THF (80 mL), and the mixture was stirred at r.t. for 16 h. The reaction mixture was concentrated in vacuo and the residue was redissolved in THF (50 mL). The reaction mixture was added dropwise to a cooled mixture of methylamine (2 M in THF, 150 mL) and H_2O (50 mL) at 0 °C, and the mixture was stirred for 16 h. The reaction mixture was concentrated in vacuo, poured into H_2O (100 mL), made basic with sat. aq $NaHCO_3$ (200 mL), extracted with EtOAc (5 × 100 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by chromatography on silica gel (heptane–EtOAc) to obtain 2-fluoro-*N*-methylbenzamide (**1c**). Yield: 4.31 g (86%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.12 (td, *J* = 7.9, 1.9 Hz, 1 H), 7.46 (dddd, *J* = 8.2, 7.3, 5.3, 1.9 Hz, 1 H), 7.30–7.22 (m, 1 H), 7.11 (ddd, *J* = 12.2, 8.3, 0.9 Hz, 1 H), 6.75 (s, 1 H), 3.04 (dd, *J* = 4.8, 1.1 Hz, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 163.9, 160.6 (d, *J* = 247 Hz), 133.2, 132.1, 124.8, 121.0 (d, *J* = 11 Hz), 116.0 (d, *J* = 25 Hz), 26.8.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for C_8H_8FNO: 154.0663; found: 154.0665.

3-Fluoro-*N*-phenylnicotinamide (1d)
Synthesized as for **1a** using 3-fluorobenzoic acid and aniline. Yield: 76%.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.66 (d, *J* = 2.7 Hz, 1 H), 8.64 (dd, *J* = 4.9, 1.4 Hz, 1 H), 8.36 (t, *J* = 22.5 Hz, 1 H), 8.03 (dd, *J* = 6.6, 4.9 Hz, 1 H), 7.66 (dd, *J* = 8.5, 0.9 Hz, 2 H), 7.44–7.38 (m, 2 H), 7.24–7.19 (m, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 159.1, 156.0 (d, *J* = 256 Hz), 147.2, 139.5 (d, *J* = 28 Hz), 136.9, 129.3, 128.0 (d, *J* = 9.6 Hz), 125.5, 124.8, 120.7.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{10}FN_2O$: 217.0772; found: 217.0774.

2-Fluoro-3-methoxy-*N*-phenylbenzamide (1e)
Synthesized as for **1a** using 2-fluoro-3-methoxybenzoic acid and aniline. Yield: 71%.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.40 (d, *J* = 14.1 Hz, 1 H), 7.70 (m, 3 H), 7.40 (t, *J* = 7.9 Hz, 2 H), 7.20 (m, 3 H), 3.97 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 161.7, 150.9 (d, *J* = 247 Hz), 148.3 (d, *J* = 13 Hz), 138.1, 129.5, 125.2, 150.0, 123.0, 120.9, 116.9, 57.0.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{13}FNO_2$: 246.0925; found: 246.0921.

***tert*-Butyl *N*′-(3-Fluoropyridine-4-carbonyl)-*N*-propylhydrazinecarboxylate (1f)**
Synthesized as for **1a** using 3-fluoronicotinic acid and *tert*-butyl *N*-propylhydrazinecarboxylate.[19] Yield: 84%.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.67–8.56 (m, 2 H), 8.32 (s, 1 H), 7.87 (s, 1 H), 3.56 (t, *J* = 7.3 Hz, 2 H), 1.67–1.58 (m, 2 H), 1.58–1.34 (m, 9 H), 0.95 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 161.1, 161.0, 156.0 (d, *J* = 259 Hz), 146.9, 139.4 (d, *J* = 27.0 Hz), 124.6, 82.0, 52.1, 28.3, 20.9, 11.2.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{20}N_3O_2$: 298.1550; found: 298.1565.

***tert*-Butyl *N*-Propylhydrazinecarboxylate**
Prepared following the literature procedure.[19]

***tert*-Butyl *N*′-(3,5-Difluoropyridine-4-carbonyl)-*N*-propylhydrazinecarboxylate (1g)**
Synthesized as for **1a** using 3,5-difluoronicotinic acid and *tert*-butyl *N*-propylhydrazinecarboxylate. Yield: 64%.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.49 (s, 2 H), 3.58 (t, *J* = 7.2 Hz, 2 H), 1.71–1.60 (m, 2 H), 1.50 (s, 9 H), 0.95 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 155.6 (d, *J* = 266 Hz), 146.3, 137.4, 137.3, 129.9, 82.4, 28.6, 21.1, 14.6, 11.6.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{20}F_2N_3O_3$: 316.1467; found: 316.1450.

***tert*-Butyl *N*′-(3-Chloro-5-fluoropyridine-4-carbonyl)-*N*-propylhydrazinecarboxylate (1h)**
Synthesized as for **1a** using 3-chloro-5-fluoronicotinic acid[20] and *tert*-butyl *N*-propylhydrazinecarboxylate. Yield: 88%.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.51 (s, 1 H), 8.47 (s, 1 H), 8.03 (s, 1 H), 3.58 (t, *J* = 7.2 Hz, 2 H), 1.71–1.60 (m, 2 H), 1.50 (s, 9 H), 0.95 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 156.9, 154.9, 154.8, 146.3, 137.4, 137.2, 129.9, 82.4, 28.6, 21.1, 14.6, 11.6.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{20}ClFN_3O_3$: 332.1177; found: 332.1177.

3-Chloro-5-fluoronicotinic Acid
Prepared following a literature procedure.[20]

Domino Reactions: General Procedure
Method A: NaHMDS (1.0 M in THF, 1.20 mL, 1.20 mmol) was added to a solution of the amide/sulfonamide (1.00 mmol) in DMF (10.0 mL) under an atmosphere of argon, and the mixture was stirred for 30 min, while cooling to 0 °C. The alkyne (2.00 mmol) was added dropwise to the mixture, which was heated by microwave irradiation using an Emry Optimizer instrument. The reaction mixture was poured into H_2O (100 mL), extracted with EtOAc–Et_2O (1:1, 3 × 100 mL), washed with diluted brine (H_2O–brine, 1:1; 3 × 100 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by chromatography on silica gel (heptane–EtOAc) to obtain the product.

Method B: NaHMDS (1.0 M in THF, 1.20 mL, 1.20 mmol) was added to a solution of the amide/sulfonamide (1.00 mmol) in DMF (10.0 mL) under an atmosphere of argon, and the mixture was stirred for 30 min, while heating to the addition temperature. A solution of the alkyne (2.00 mmol) in DMF (5.0 mL) was added dropwise to the mixture at a rate of 0.4 mL/h, while continuing the heating. The reaction mixture was cooled to r.t. and poured into H_2O (100 mL), extracted with EtOAc–Et_2O (1:1, 3 × 100 mL), washed with diluted brine (H_2O–brine, 1:1; 3 × 100 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by chromatography on silica gel (heptane–EtOAc).

Ethyl 5-Oxo-6,7-diphenyl-5,6-dihydro-1,6-naphthyridine-8-carboxylate (3a)

Synthesized by method A using 2-fluoro-*N*-phenylnicotinamide (**1a**) and ethyl phenylpropiolate (**2a**). Heating for 4 h at 200 °C. Yield: 65%.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.81 (dt, *J* = 16.6, 8.3 Hz, 1 H), 8.62 (dd, *J* = 4.4, 1.8 Hz, 1 H), 7.37 (tt, *J* = 15.7, 7.9 Hz, 2 H), 7.32–7.23 (m, 4 H), 7.22–7.15 (m, 3 H), 7.12–7.05 (m, 2 H), 4.01 (q, *J* = 7.1 Hz, 2 H), 0.91 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 175.1, 165.9, 153.2, 151.7, 138.6, 136.3, 133.2, 130.3, 129.5, 129.3, 129.1, 128.8, 128.0, 121.2, 120.7, 120.2, 61.4, 13.9.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{19}N_2O_3$: 371.1390; found: 371.1392.

Ethyl 1-Oxo-2,3-diphenyl-1,2-dihydroisoquinoline-4-carboxylate (3b)

Synthesized by method A using 2-fluoro-*N*-phenylbenzamide (**1b**) and ethyl phenylpropiolate (**2a**). Heating for 4 h at 200 °C. Yield: 61%.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.54 (dd, *J* = 8.1, 1.4 Hz, 1 H), 7.48 (ddd, *J* = 8.7, 7.0, 1.7 Hz, 1 H), 7.40 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1 H), 7.37–7.28 (m, 3 H), 7.22–7.14 (m, 5 H), 7.14–7.08 (m, 2 H), 6.80 (d, *J* = 8.5 Hz, 1 H), 4.01 (q, *J* = 7.1 Hz, 2 H), 0.94–0.89 (m, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.5, 166.3, 151.8, 146.7, 142.0, 138.5, 133.2, 132.4, 130.0, 129.6, 129.5, 129.2, 128.9, 127.7, 126.7, 126.1, 124.4, 119.0, 118.2, 61.0, 13.8.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{20}NO_3$: 370.1438; found: 370.1439.

Ethyl 2-Methyl-1-oxo-3-phenyl-1,2-dihydroisoquinoline-4-carboxylate (3c)

Synthesized by method A using 2-fluoro-*N*-methyl-benzamide (**1c**) and ethyl phenylpropiolate (**2a**). Heating for 4 h at 200 °C. Yield: 52%.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.55 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.74 (ddd, *J* = 8.7, 7.1, 1.7 Hz, 1 H), 7.55 (d, *J* = 8.6 Hz, 1 H), 7.53–7.48 (m, 3 H), 7.46 (ddd, *J* = 8.0, 7.1, 0.9 Hz, 1 H), 7.44–7.40 (m, 2 H), 3.99 (q, *J* = 7.1 Hz, 2 H), 3.54 (s, 3 H), 0.92 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 174.1, 166.3, 152.2, 141.2, 133.6, 132.9, 129.9, 128.8, 127.3, 126.9, 124.3, 119.3, 115.9, 100.0, 60.9, 37.1, 13.8.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{18}NO_3$: 308.1281; found: 308.1291.

Ethyl 1-Oxo-2,3-diphenyl-1,2-dihydro-2,6-naphthyridine-4-carboxylate (3d)

Synthesized by method A using 3-fluoro-*N*-phenylnicotinamide (**1d**) and ethyl phenylpropiolate (**2a**). Heating for 4 h at 200 °C. Yield: 40%.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.61 (d, *J* = 5.2 Hz, 1 H), 8.35 (s, 1 H), 8.29 (dd, *J* = 5.2, 0.8 Hz, 1 H), 7.42–7.32 (m, 3 H), 7.25–7.13 (m, 7 H), 4.02 (q, *J* = 7.1 Hz, 2 H), 0.92 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 173.4, 165.5, 152.7, 143.9, 142.2, 137.3, 137.2, 132.4, 130.3, 129.9, 129.7, 129.4, 127.9, 120.3, 118.2, 61.3, 13.7.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{19}N_2O_3$: 371.1390; found: 371.1398.

Ethyl 5-Methoxy-1-oxo-2,3-diphenyl-1,2-dihydroisoquinoline-4-carboxylate (3e)

Synthesized by method A using 2-fluoro-3-methoxy-*N*-phenylbenzamide (**1e**) and ethyl phenylpropiolate (**2a**). Heating for 4 h at 200 °C. Yield: 63%.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.20 (d, *J* = 8.1 Hz, 1 H), 7.38 (t, *J* = 8.0 Hz, 1 H), 7.22–7.10 (m, 8 H), 7.06 (d, *J* = 7.9 Hz, 1 H), 7.00 (m, 2 H), 3.99 (q, *J* = 7.1 Hz, 2 H), 3.29 (s, 3 H), 0.92 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 174.8, 166.5, 153.7, 150.4, 143.8, 133.8, 133.4, 130.2, 129.2, 129.1, 129.0, 128.1, 127.8, 127.8, 125.4, 119.2, 116.1, 61.3, 56.7, 14.1.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{22}NO_4$: 400.1543; found: 400.1539.

Ethyl 7-Methyl-5-oxo-6-phenyl-5,6-dihydro-1,6-naphthyridine-8-carboxylate (3f)

Synthesized by method B using 2-fluoro-*N*-phenylnicotinamide (**1a**) and ethyl 2-butynoate (**2b**). Heating at 150 °C for 16 h. Yield: 48%.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.95 (dt, *J* = 4.6, 2.3 Hz, 1 H), 8.61 (dd, *J* = 8.0, 1.9 Hz, 1 H), 7.59–7.54 (m, 2 H), 7.53–7.48 (m, 1 H), 7.40 (dt, *J* = 8.0, 4.0 Hz, 1 H), 7.26–7.22 (m, 2 H), 4.51 (q, *J* = 7.2 Hz, 2 H), 2.08 (s, 3 H), 1.43 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 167.4, 162.8, 155.1, 151.1, 142.3, 138.0, 136.4, 130.0, 129.3, 128.3, 121.9, 120.2, 114.4, 61.9, 19.5, 14.3.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{17}N_2O_3$: 309.1234; found: 309.1238.

Ethyl 2-(*tert*-Butoxycarbonylpropylamino)-3-methyl-1-oxo-1,2-dihydro-2,6-naphthyridine-4-carboxylate (3g)

Synthesized by method B using *tert*-butyl *N*′-(3-fluoropyridine-4-carbonyl)-*N*-propylhydrazinecarboxylate (**1f**) and ethyl 2-butynoate (**2b**). Heating at 100 °C for 16 h. Yield: 41%.

^{1}H NMR (600 MHz, $CDCl_3$): δ (mixtures of two rotamers) = 9.35 (d, *J* = 8.1 Hz, 1 H), 8.70 (dd, *J* = 10.9, 5.5 Hz, 1 H), 8.36 (dd, *J* = 5.4, 3.2 Hz, 1 H), 4.62–4.42 (m, 2 H), 3.88–3.76 (m, 1 H), 3.47–3.38 (m, 1 H), 2.53 (d, *J* = 7.3 Hz, 3 H), 1.71–1.51 (m, 6 H), 1.46 (dt, *J* = 16.0, 7.1 Hz, 3 H), 1.35 (s, 5 H), 0.93 (dt, *J* = 11.4, 7.4 Hz, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ (mixtures of two rotamers) = 158.6, 153.7, 145.9, 145.7, 142.5, 141.9, 129.5, 122.3, 83.5, 82.8, 62.5, 53.1, 51.7, 28.2, 27.9, 21.5, 20.9, 17.3, 14.2, 11.4.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{28}N_3O_5$: 390.2033; found: 390.2012.

Ethyl 2-(*tert*-Butoxycarbonylpropylamino)-8-fluoro-3-methyl-1-oxo-1,2-dihydro-2,6-naphthyridine-4-carboxylate (3h)

Synthesized by method B using *tert*-butyl *N*′-(3,5-difluoropyridine-4-carbonyl)-*N*-propylhydrazinecarboxylate (**1g**) and ethyl 2-butynoate (**2b**). Heating at 100 °C for 16 h. Yield: 24%.

^{1}H NMR (500 MHz, $CDCl_3$): δ (mixtures of two rotamers) = 8.92 (d, *J* = 15.2 Hz, 1 H), 8.50 (d, *J* = 13.8 Hz, 1 H), 4.51 (m, 2 H),

3.94–3.74 (m, 1 H), 3.49–3.34 (m, 1 H), 2.47 (d, *J* = 6.6 Hz, 3 H), 1.76–1.57 (m, 2 H), 1.57 (s, 5 H), 1.46 (m, 3 H), 1.38 (s, 4 H), 0.94 (q, *J* = 7.3 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ (mixtures of two rotamers) = 166.3, 156.6, 156.4, 154.9, 154.7, 147.8, 147.6, 143.8, 134.9, 134.7, 83.6, 83.0, 62.7, 62.5, 53.5, 52.0, 28.6, 28.4, 21.9, 21.4, 17.5, 17.3, 14.6, 11.7, 11.6.

HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{27}FN_3O_5$: 408.1929; found: 408.1937.

Ethyl 2-(*tert*-Butoxycarbonylpropylamino)-8-chloro-3-methyl-1-oxo-1,2-dihydro-2,6-naphthyridine-4-carboxylate (3i)

Synthesized by method B using *tert*-butyl *N*′-(3-chloro-5-fluoropyridine-4-carbonyl)-*N*-propylhydrazinecarboxylate (**1h**) and ethyl 2-butynoate (**2b**). Heating at 100 °C for 16 h. Yield: 18%.

^{1}H NMR (500 MHz, $CDCl_3$): δ (mixtures of two rotamers) = 8.92 (d, *J* = 16.7 Hz, 1 H), 8.63 (d, *J* = 13.3 Hz, 1 H), 4.50 (m, 3 H), 3.95–3.79 (m, 1 H), 3.44–3.29 (m, 1 H), 2.45 (d, *J* = 8.5 Hz, 3 H), 1.72–1.63 (m, 2 H), 1.57 (s, 5 H), 1.50–1.43 (m, 3 H), 1.39 (s, 4 H), 0.94 (m, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ (mixtures of two rotamers) = 166.1, 166.0, 157.4, 157.2, 154.5, 154.4, 147.5, 147.4, 146.8, 146.6, 145.9, 145.8, 130.9, 130.7, 130.5, 125.8, 125.5, 108.3, 108.1, 83.2, 82.6, 62.3, 62.2, 53.0, 51.7, 29.7, 28.2, 27.9, 21.7, 21.1, 17.2, 16.9, 14.2, 14.2, 11.4, 11.3.

HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{27}ClN_3O_5$: 424.1634; found: 424.1642.

***tert*-Butyl 7-Methyl-5-oxo-6-phenyl-5,6-dihydro-1,6-naphthyridine-8-carboxylate (3j)**

Synthesized by method A using 2-fluoro-*N*-phenylnicotinamide (**1a**) and ethyl hexynoate (**2c**). Heating for 4 h at 200 °C. Yield: 53%.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.96 (dd, *J* = 4.6, 1.7 Hz, 1 H), 8.62 (dd, *J* = 8.0, 1.7 Hz, 1 H), 7.56 (m, 3 H), 7.42 (dd, *J* = 8.0, 4.6 Hz, 1 H), 7.30 (m, 2 H), 4.54 (q, *J* = 7.1 Hz, 2 H), 2.49–2.37 (m, 2 H), 1.52 (dt, *J* = 11.8, 7.6 Hz, 2 H), 1.45 (t, *J* = 7.1 Hz, 3 H), 0.72 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 167.8, 163.4, 155.5, 151.7, 146.7, 137.9, 136.8, 130.1, 129.6, 129.2, 122.3, 120.6, 114.7, 62.24, 34.2, 23.1, 14.7, 14.5.

HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{21}N_2O_3$: 337.1547; found: 337.1551.

2-Fluoropyridine-3-sulfonic Acid Phenylamide (4a)

2-Fluoropyridine-3-sulfonyl chloride[21] (0.71 g, 3.6 mmol) was added to pyridine (100 mL) under an atmosphere of argon, and the mixture was cooled to 0 °C. Aniline (0.35 mL, 3.8 mmol) was added, and the mixture was stirred for 16 h while returning to r.t. The reaction mixture was concentrated in vacuo and the residue was purified by chromatography on silica gel (heptane–EtOAc) to obtain 2-fluoropyridine-3-sulfonic acid phenylamide (**4a**). Yield: 0.76 g (84%).

^{1}H NMR (600 MHz, DMSO): δ = 10.85 (s, 1 H), 8.47 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1 H), 8.36 (ddd, *J* = 9.6, 7.6, 1.9 Hz, 1 H), 7.54 (ddd, *J* = 7.6, 4.9, 1.6 Hz, 1 H), 7.28–7.21 (m, 2 H), 7.14–7.09 (m, 2 H), 7.09–7.00 (m, 1 H).

^{13}C NMR (151 MHz, DMSO): δ = 158.1 (d, *J* = 242 Hz), 152.9 (d, *J* = 15 Hz), 142.8, 137.1, 129.8, 125.1, 123.5, 122.7 (d, *J* = 30 Hz), 120.63.

2-Fluoropyridine-3-sulfonyl Chloride

Prepared according to the literature procedure.[21]

2,6-Difluoro-*N*-phenylbenzenesulfonamide (4b)

Synthesized as for **4a** using 2,6-difluorobenzenesulfonyl chloride and aniline. Yield: 85%.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.49 (tt, *J* = 8.4, 6.0 Hz, 1 H), 7.29 (dd, *J* = 9.2, 6.5 Hz, 2 H), 7.20 (d, *J* = 7.8 Hz, 2 H), 7.16 (t, *J* = 7.4 Hz, 1 H), 7.01 (m, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 160.2 (d, *J* = 259 Hz), 135.9, 135.4 (t, *J* = 11 Hz), 129.9, 126.3, 121.5, 117.1, 113.5 (d, *J* = 23 Hz).

2-Fluoro-*N*-phenylbenzenesulfonamide (4c)

Synthesized as for **4a** using 2-fluorobenzenesulfonyl chloride and aniline. Yield: 79%.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.82 (t, *J* = 7.5 Hz, 1 H), 7.53 (ddd, *J* = 8.3, 7.4, 5.1 Hz, 1 H), 7.25–7.15 (m, 4 H), 7.14–7.07 (m, 3 H), 6.74 (s, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 158.7 (d, *J* = 254 Hz), 135.6, 135.5, 131.0, 129.4, 125.8, 124.6, 121.6, 116.9.

2-Fluoro-*N*-methylbenzenesulfonamide (4d)

2-Fluorobenzenesulfonyl chloride (0.70 mL, 5.3 mmol) was dissolved in THF (50 mL), and the mixture was cooled to 0 °C. Methylamine (2.0 M in THF, 8.0 mL, 16 mmol) was added dropwise, and the mixture was stirred for 1 h. The mixture was concentrated in vacuo, dissolved in Et_2O (50 mL), washed with 1 M HCl (2 × 50 mL) and brine (2 × 50 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by chromatography on silica gel (heptane–EtOAc) to obtain 2-fluoro-*N*-methylbenzenesulfonamide (**4c**). Yield: 0.77 g (77%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.92 (td, *J* = 7.7, 1.5 Hz, 1 H), 7.61 (ddd, *J* = 7.8, 5.2, 1.5 Hz, 1 H), 7.31 (t, *J* = 7.6 Hz, 1 H), 7.27–7.19 (m, 1 H), 4.81 (d, *J* = 3.5 Hz, 1 H), 2.72 (d, *J* = 5.3 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 159.2 (d, *J* = 254 Hz), 135.5, 131.2, 127.1, 124.9, 117.4, 29.7.

Ethyl 1,1-Dioxo-2,3-diphenyl-1,2-dihydro-1(6)-thia-2,5-diazanaphthalene-4-carboxylate (5a)

Synthesized by method A using 2-fluoropyridine-3-sulfonic acid phenylamide (**4a**) and ethyl 2-butynoate (**2b**). Heating for 1 h at 200 °C. Yield: 64%.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.89 (dd, *J* = 4.8, 1.4 Hz, 1 H), 8.14 (dd, *J* = 8.0, 1.4 Hz, 1 H), 7.53–7.46 (m, 3 H), 7.43 (dd, *J* = 7.9, 4.8 Hz, 1 H), 7.31 (dd, *J* = 6.3, 3.2 Hz, 2 H), 4.48 (q, *J* = 7.1 Hz, 2 H), 2.14 (s, 3 H), 1.41 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 166.9, 153.7, 149.3, 134.9, 130.9, 130.1, 130.0, 129.6, 127.5, 122.4, 118.9, 62.3, 19.8, 14.6.

HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{17}N_2O_4S$: 345.0904; found: 345.0904.

Ethyl 8-Fluoro-3-methyl-1,1-dioxo-2-phenyl-1,2-dihydro-1λ(6)-1,2-benzothiazine-4-carboxylate (5b)

Synthesized by method A using 2,6-difluoro-*N*-phenylbenzenesulfonamide (**4b**) and ethyl 2-butynoate (**2b**). Heating for 1 h at 200 °C. Yield: 75%.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.60 (td, *J* = 8.2, 5.3 Hz, 1 H), 7.47–7.40 (m, 4 H), 7.27 (dd, *J* = 6.7, 2.9 Hz, 2 H), 7.23–7.16 (m, 1 H), 4.43 (q, *J* = 7.1 Hz, 2 H), 2.12 (s, 3 H), 1.41 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 167.2, 159.5 (d, *J* = 245 Hz), 143.2, 135.4, 133.8, 133.7, 129.9, 129.7, 129.4, 122.2, 117.3, 115.8, 115.6, 113.4, 107.9, 62.3, 20.2, 14.5.

HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{17}FNO_4S$: 362.0857; found: 362.0864.

Ethyl 3-Methyl-1,1-dioxo-2-phenyl-1,2-dihydro-1λ(6)-1,2-benzothiazine-4-carboxylate (5c)

Synthesized by method B using 2-fluoro-*N*-phenylbenzenesulfonamide (**4c**) and ethyl 2-butynoate (**2b**). Heating at 150 °C for 16 h. Yield: 38%.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 7.8 Hz, 1 H), 7.68–7.62 (m, 2 H), 7.52–7.48 (m, 1 H), 7.44–7.38 (m, 3 H), 7.25–7.22 (m, 2 H), 4.41 (q, *J* = 7.1 Hz, 2 H), 2.13 (s, 3 H), 1.39 (dd, *J* = 8.5, 5.8 Hz, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 167.0, 142.5, 135.2, 132.3, 131.3, 130.9, 129.5, 129.2, 128.9, 127.9, 126.1, 122.3, 116.6, 61.8, 19.8, 14.2.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{18}NO_4S$: 344.0951; found: 344.0951.

Ethyl 2-Methyl-1,1-dioxo-3-phenyl-1,2-dihydro-1λ(6)-1,2-benzothiazine-4-carboxylate (5d)

Synthesized by method A using 2-fluoro-*N*-methylbenzenesulfonamide (**4d**) and ethyl phenylpropiolate (**2a**). Heating for 4 h at 200 °C. Yield: 46%.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.19 (d, *J* = 8.2 Hz, 1 H), 7.95 (dd, *J* = 7.8, 1.3 Hz, 1 H), 7.71–7.65 (m, 1 H), 7.59–7.52 (m, 3 H), 7.50–7.45 (m, 3 H), 3.89 (q, *J* = 7.1 Hz, 2 H), 3.02 (s, 3 H), 0.75 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 167.1, 146.0, 134.1, 132.3, 130.7, 130.3, 129.2, 129.0, 128.8, 128.2, 126.0, 121.9, 116.0, 61.3, 34.8, 13.3.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{18}NO_4S$: 344.0951; found: 344.0952.

Ethyl 8-Fluoro-1,1-dioxo-2-phenyl-3-trifluoromethyl-1,2-dihydro-1λ(6)-1,2-benzothiazine-4-carboxylate (5e)

Synthesized by method B using 2,6-difluoro-*N*-phenylbenzenesulfonamide (**4b**) and ethyl 4,4,4-trifluoro-2-butynoate (**2d**). Heating at 150 °C for 16 h. Yield: 36%.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.71 (td, *J* = 8.3, 5.1 Hz, 1 H), 7.51 (d, *J* = 8.0 Hz, 1 H), 7.40–7.33 (m, 4 H), 7.18–7.13 (m, 2 H), 4.46 (q, *J* = 7.2 Hz, 2 H), 1.40 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 163.8, 157.7 (d, *J* = 261 Hz), 135.7, 134.4 (d, *J* = 9 Hz), 130.5, 129.6, 129.4, 127.4, 127.2, 123.5 (d, *J* = 4 Hz), 122.5 (d, *J* = 15 Hz), 121.0, 119.6 (d, *J* = 21 Hz), 119.1, 63.4, 13.9.

HRMS (EI): *m*/*z* [M + NH_4^+] calcd for $C_{18}H_{17}F_4N_2O_4S$: 433.0834; found: 433.0847.

Ethyl 3-[(2-Fluorobenzoyl)methylamino]butyrate (6a)

Ethyl 3-(methylamino)butynoate (0.55 g, 3.8 mmol) was added to 2-fluorobenzoic acid (0.50 g, 3.56 mmol), *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (0.77 g, 4.0 mmol) and 1-hydroxybenzotriazole (0.50 g, 3.7 mmol) in THF (20 mL). The reaction mixture was stirred at r.t. for 16 h then the mixture was poured into H_2O (20 mL), extracted with EtOAc (3 × 50 mL), washed with sat. aq $NaHCO_3$ (3 × 50 mL) and brine (3 × 50 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by chromatography on silica gel (heptane–EtOAc) to obtain **6a**. Yield: 0.21 g (22%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.43–7.30 (m, 2 H), 7.23–7.16 (m, 1 H), 7.13–7.03 (m, 1 H), 5.21–5.12 (m, 1 H), 4.20–4.09 (m, 2 H), 2.99 (s, 3 H), 2.72–2.66 (m, 1 H), 2.55 (m, 1 H), 1.31 (d, *J* = 6.7 Hz, 2 H), 1.30–1.19 (m, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 170.9, 166.8, 158.9, 131.1, 128.9, 125.2, 124.5, 115.8, 60.8, 51.3, 47.0, 18.8, 17.6, 14.2.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{19}FNO_3$: 268.1343; found: 268.1331.

Ethyl 3-[(2,6-Difluorobenzenesulfonyl)methylamino]butyrate (6b)

Ethyl 3-(methylamino)butynoate (0.74 g, 5.1 mmol) and *N*,*N*-diisopropylethylamine (0.97 mL, 5.6 mmol) were dissolved in THF (50 mL) and cooled to 0 °C. 2,6-Difluorobenzenedulfonyl chloride (1.05 g, 4.9 mmol) was added and the reaction mixture was allowed to return to r.t. while stirring overnight. The reaction mixture was filtered and concentrated in vacuo and the crude product was purified by chromatography on silica gel (heptane–EtOAc) to obtain **6b**. Yield: 0.60 g (38%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.49 (tt, *J* = 8.4, 5.9 Hz, 1 H), 7.01 (t, *J* = 8.5 Hz, 2 H), 4.61–4.53 (m, 1 H), 4.09–4.01 (m, 2 H), 2.91 (s, 3 H), 2.53 (dd, *J* = 14.9, 7.1 Hz, 1 H), 2.44 (dd, *J* = 14.9, 7.7 Hz, 1 H), 1.24 (t, *J* = 7.2 Hz, 3 H), 1.17 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 170.3, 159.7 (dd, *J* = 258.6, 4.2 Hz), 134.2 (t, *J* = 11.0 Hz), 118.3 (t, *J* = 16.3 Hz), 113.1 (dd, *J* = 23.8, 3.7 Hz), 60.8, 50.5, 39.8, 28.1, 17.8, 14.1.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{18}F_2NO_4S$: 322.0919; found: 322.0908.

2-Fluoro-*N*-methylbenzamide (1c) by Retro-Conjugate Addition

NaHMDS (2.0 M in THF, 0.100 mL, 0.200 mmol) was added to a solution of ethyl 3-[(2-fluorobenzoyl)methylamino]butyrate (**6a**; 49 mg, 0.18 mmol) in DMF (2.0 mL). The mixture was stirred at r.t. for 1 h, then concentrated in vacuo and the crude mixture was purified by chromatography on silica gel (heptane–EtOAc) to obtain **1c**. Yield: 89%.

NMR spectra matched those obtained previously.

2,6-Difluoro-*N*-methyl-benzenesulfonamide (7)

Synthesized above using ethyl 3-[(2,6-difluorobenzenesulfonyl)methylamino]butyrate (**6b**). Yield: 91%.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.60–7.50 (m, 1 H), 7.07 (t, *J* = 8.9 Hz, 2 H), 4.98 (s, 1 H), 2.83 (d, *J* = 5.3 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 160.0 (d, *J* = 258 Hz), 135.1 (dd, *J* = 81, 70 Hz), 117.5 (t, *J* = 16 Hz), 113.5 (d, *J* = 24 Hz), 29.8.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_7H_8F_2NO_2S$: 208.0238; found: 208.0230.

2,3-Diphenyl-2*H*-isoquinolin-1-one (9)

Ethyl 1-Oxo-2,3-diphenyl-1,2-dihydroisoquinoline-4-carboxylate (**3b**; 51 mg, 0.14 mmol) was dissolved in a mixture of MeOH (1.0 mL) and aq NaOH (2.00 M, 0.20 mL). The mixture was heated to reflux for 2 h then aq HCl (1 M) was added until pH 3–4 was reached. The mixture was extracted with EtOAc (3 × 10 mL) and concentrated in vacuo. The residue was dissolved in a mixture of *N*-methylpyrrolidinone (3 mL) and quinoline (1.5 mL). To this mixture was added copper(I) oxide (2 mg, 0.01 mmol) and *o*-phenanthroline (6 mg, 0.03 mmol) under an atmosphere of argon. The reaction mixture was heated by microwave irradiation using an Emry Optimizer instrument (1 h at 190 °C). The mixture was diluted with aq HCl (1 M, 10 mL), extracted with EtOAc–Et_2O (1:1, 3 × 10 mL), washed with a H_2O–brine mixture (1:1, 3 × 10 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by chromatography on silica gel (heptane–EtOAc) to obtain 2,3-diphenyl-2*H*-isoquinolin-1-one (**9**). Yield: 36 mg (89%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.52 (dd, *J* = 8.1, 1.7 Hz, 1 H), 7.48 (ddd, *J* = 8.7, 7.0, 1.7 Hz, 1 H), 7.41–7.31 (m, 4 H), 7.22–7.14 (m, 7 H), 6.91 (d, *J* = 8.3 Hz, 1 H), 6.45 (s, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 177.9, 153.9, 142.6, 139.2, 135.7, 131.9, 130.1, 129.6, 129.2, 128.9, 128.6, 127.9, 126.3, 126.1, 123.8, 118.1, 112.6.

HRMS (EI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{16}NO$: 298.1226; found: 298.1225.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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