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ACETATE/ACETIC ACID-ASSISTED ONE-POT SYNTHESIS OF (DIARYLMETHYLENE)IMIDAZOLONE FROM AMIDE OR THIOAMIDE

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Abstract – With the aim of extending the library of green fluorescent protein chromophore analogs, a facile one-pot synthesis of 5-(diarylmethylene)imidazolones from the corresponding amide or thioamide is described. Isolation of unstable imidate intermediates is not required, thereby circumventing the drawback of previous approaches. A reaction mechanism in which both acetate and acetic acid promote the imidazolone formation is proposed.

Imidazolone, also called imidazolinone, is a common heterocycle found in the chromophore structure of representative fluorescent proteins such as green fluorescent protein (GFP), blue fluorescent protein (BFP), cyan fluorescent protein (CFP), and Sirius protein (Figure 1).[1] In addition, imidazolone is attractive as a constituent unit of bioactive agents including irbesartan and imazapic.[2] Therefore, numerous imidazolone-containing compounds have been developed so far; especially, 5-arylmethylenated imidazolones have attracted significant attention because of its practical use as fluorescent dyes analogous to the GFP chromophore (GFPc).[3]

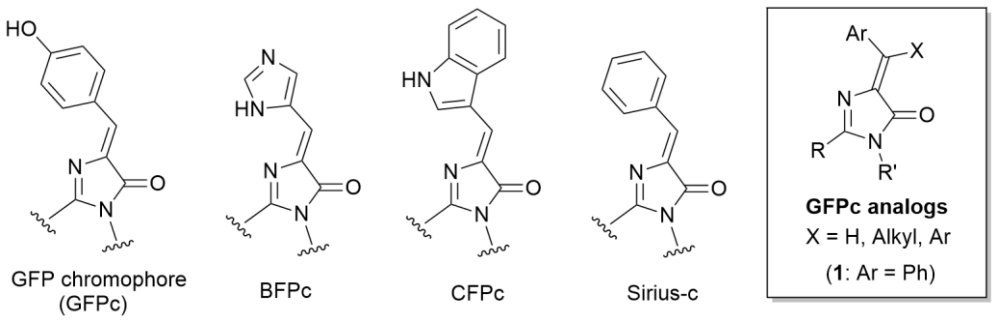
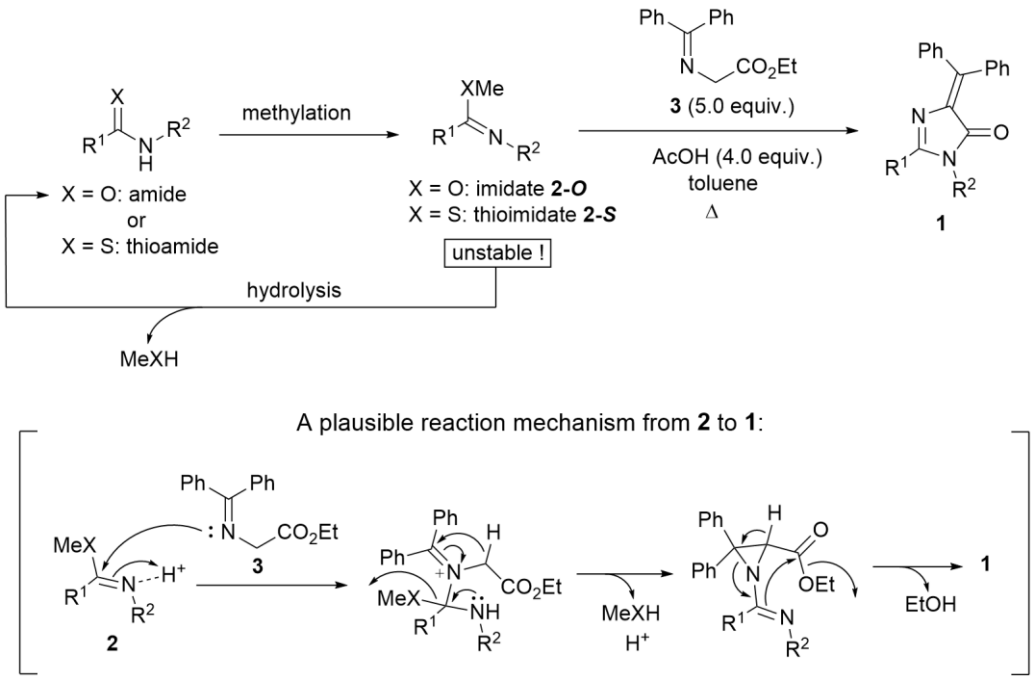


Figure 1. Structures of green fluorescent protein chromophore (GFPc) and its analogs

We previously developed a diaryl analog of GFPc (X = Ar, Figure 1), namely, (diarylmethylene)imidazolinone (DAIN), which can act as a fluorescent molecular rotor.[4,5] In particular, the diphenyl derivative **1** showed notable fluorescence properties such as viscosity-dependent emission and aggregation-induced emission.[4–7] The DAIN structure was readily synthesized by a condensation reaction developed in our group (Scheme 1).[4,5] This reaction produces the DAIN ring in moderate yields (about 40%–80%) by mixing imidate **2-*O*** (or thioimidate **2-*S***) and iminoacetate **3** in the presence of acetic acid. This reaction proceeds most likely by migration of the diphenylmethylene moiety from nitrogen to the α-carbon of the same molecule via an aziridine intermediate. Acetic acid enhances the electrophilicity of the imidate by protonation to the imino nitrogen. Certainly, this condensation reaction is a promising tool for the DAIN synthesis; however, some drawbacks need to be overcome, particularly those regarding the hydrolytic instability of imidate **2**. In addition, the low boiling point of small imidate molecules renders them more difficult to handle. Thus, we were interested in improving the synthetic method to DAIN **1** by circumventing the isolation of the unstable imidate **2**. In this paper, we report an improved synthesis of DAIN from the corresponding amide or thioamide by a one-pot procedure that does not require isolation of an imidate intermediate.

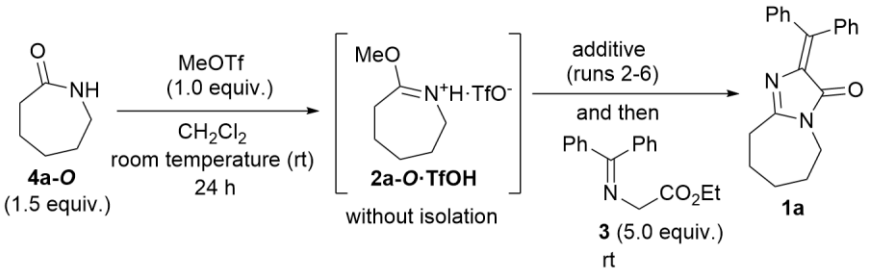


Scheme 1. Stepwise synthesis of **1** and a plausible reaction mechanism from **2** to **1**

As a first attempt, we added iminoacetate **3** to the methylation mixture with amide **4a-*O*** and methyl triflate (MeOTf), as expecting that trifluoromethanesulfonic acid (TfOH) generated *in situ* could serve as a proton source to activate the imino nitrogen of **2a-*O*** (run 1, Table 1). This hypothesis was based on the reaction mechanism of the DAIN synthesis, in which acetic acid enhances the electrophilicity of the

imidate. However, contrary to our expectation, DAIN **1a** was not obtained under these conditions. We then sought to reduce the acidity of TfOH by adding a mild base such as pyridine or triethylamine to the reaction mixture after the methylation of **4a-*O***; however, these attempts were also ineffective (runs 2 and 3, Table 1). Considering then that an acetoxy group might be necessary for this reaction, acetoxy compounds were evaluated as additives (runs 4–6, Table 1). Consequently, basic acetoxy groups afforded a small amount of **1a**, whereas acetic acid proved ineffective (runs 5 and 6 vs. 4, Table 1), which indicates that replacement of TfO^- with AcO^- was crucial for the reaction. Eventually, addition of the tetramethylammonium salt as acetoxy source gave the best result, although the yield was still quite low (run 6, Table 1).

Table 1. Effect of additives in the synthesis of **1a**

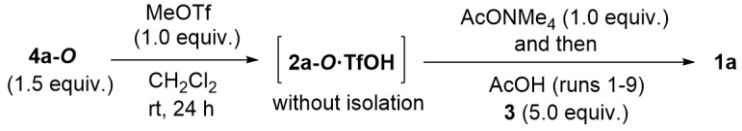


Run	Additive (1.0 equiv.)	TLC after 24 h	Yield after 48 h (%)
1	none	not detected	—
2	pyridine	not detected	—
3	Et_3N	not detected	—
4	AcOH	not detected	—
5	AcONa	trace	< 4
6	$AcONMe_4$	detected	8

To improve the product yield, we then added acetic acid to the reaction mixture described in run 6 in Table 1. The result is shown in Table 2. Notably, the addition of acetic acid was found to improve the yield effectively (runs 1–6, Table 2); in particular, around ten equivalents of acetic acid seemed the appropriate amount, affording a yield of 52% (run 4, Table 2). The yield could not be further improved by extending the reaction time (run 4 vs. 6, Table 2), but refluxing in 1,2-dichloroethane allowed shortening the reaction time (run 4 vs. 7, Table 2). Using a different carboxylic acid reduced the yield (run 4 vs. 8, Table 2). Under excess acetic acid conditions, **1a** was yielded even without tetramethylammonium acetate; however, its yield was considerably low (run 9, Table 2).[8] Since the previous method afforded **1a** in 60% yield from isolated **2a-*O***,[5] the yield of 52% obtained following the present procedure can be

considered acceptable. In addition, the total yield of this one-pot method is superior to that of the corresponding stepwise synthesis from **4a-*O*** (15% total yield; methylation: 25%; condensation: 60%).

Table 2. Effect of the addition of acetic acid for the synthesis of **1a**



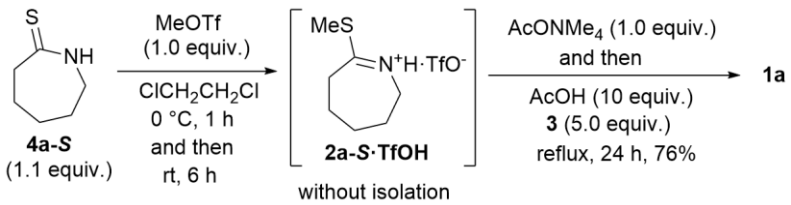
Run	Equiv. of AcOH	Temp.	Time (h)	Yield (%)
1	1	rt	48	18
2	3	rt	48	42
3	5	rt	48	37
4	10	rt	48	52
5	20	rt	48	51
6	10	rt	72	54
7	10	reflux[a]	24	52
8	10[b]	rt	48	44
9	11	rt	48	6[c]

[a] 1,2-Dichloroethane was used as the solvent.

[b] $EtCO_2H$ was used instead of AcOH.

[c] The reaction was performed without $AcONMe_4$.

Notably, the refluxing condition (run 7, Table 2) was also applicable to the corresponding thiolactam **4a-*S***, improving the yield of **1a** to 76% (Scheme 2). Besides, the amount of thiolactam could be reduced to 1.1 equivalents due to the high nucleophilicity of the sulfur atom. Meanwhile, the room temperature conditions did not improve the yield of **1a** (conditions: 10 equiv. of AcOH, rt, 48 h, 47% yield).

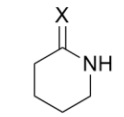
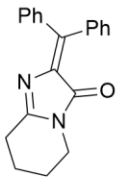
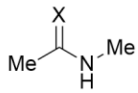
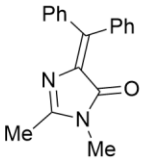
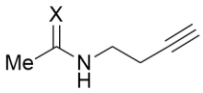
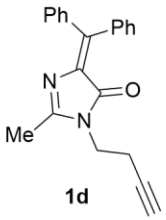
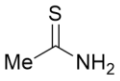
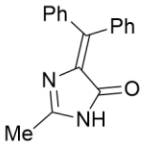


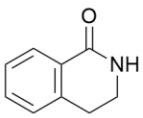
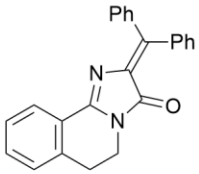
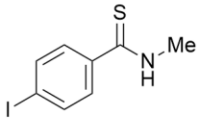
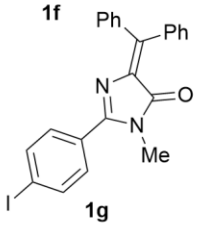
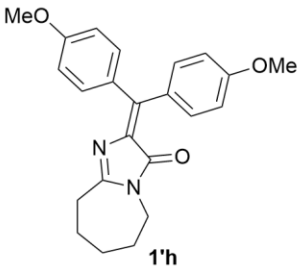
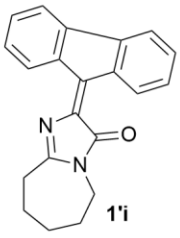
Scheme 2. Synthesis of **1a** from thiolactam **4a-*S***

Next, a substrate screening was performed using the optimized one-pot methods, method A (from amide at rt or under reflux) and B (from thioamide under reflux). A variety of DAINs including

low-molecular-weight analogs **1b**–**e** were prepared (Table 3). The products were obtained in moderate yields by either method. Although thioamides **4-*S*** generally afforded good yields, amides **4-*O*** also afforded acceptable yields in the case of cyclic structures. The use of amide is an efficient choice for the short synthesis of **1** because it does not require a thioamidation step. Low yields from acyclic amides such as **4c-*O*** and **4d-*O*** are presumably due to their weak reactivity to MeOTf. Notably, this one-pot reaction was applicable for the synthesis of not only diphenyl analogs but also diaryl analogs **1′h** and **1′i** using the corresponding iminoacetates.

Table 3. Examples of the one-pot synthesis of **1** from a variety of amides and/or thioamides

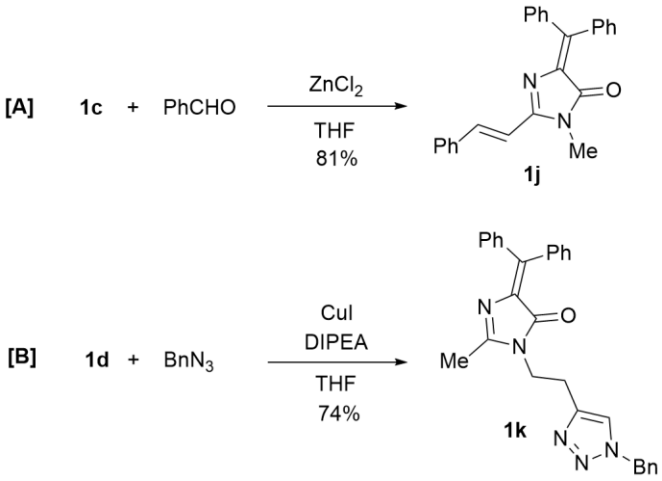
Amide	DAIN	Yield (%) [method A/B][a]
 X = O: **4b-*O*** X = S: **4b-*S***	 **1b**	49 [A, rt] 49 [B]
 X = O: **4c-*O*** X = S: **4c-*S***	 **1c**	15 [A, reflux] 47 [B]
 X = O: **4d-*O*** X = S: **4d-*S***	 **1d**	14 [A, reflux] 41 [B]
 **4e-*S***	 **1e**	50 [B]

Amide	DAIN	Yield (%) [method A/B][a]
 **4f-*O***	 **1f**	63 [A, reflux]
 **4g-*S***	 **1g**	54 [B]
4a-*O*	 **1'h**	51 [A, rt]
4a-*O*	 **1'i**	41 [A, rt]

[a] Method A: from amide at rt or under reflux; method B: from thioamide under reflux.

A notable advantage of this reaction is the facile synthesis of small size analogs such as **1c** and **1d**, which can extend the library of GFPc analogs. For example, **1c** can be utilized as a common substrate for aldol-type condensation reactions, affording red-Kaede-type chromophore analogs possessing an extended conjugation system at the 2-position.[9,10] These analogs produce a red shift of fluorescence. An

example of this reaction is shown in Scheme 3-A; styryl analog **1j** was successfully obtained by the condensation of **1c** with benzaldehyde in the presence of zinc chloride in good yield.[9] Furthermore, **1d** was applicable to the click chemistry reaction shown in Scheme 3-B,[11] which suggests that DAIN **1** can be applied to fluorescent probes in the chemical biology field.[12]



Scheme 3. Application of small size analogs **1c** and **1d** as substrates

According to our results, we reconsidered the reaction mechanism as follows (Figure 2). Since the first attempt using **2a·TfOH** and **3** was unsuccessful, replacement of TfO^- as the counter anion with AcO^- seems critical to the process, which suggests that the formation of the aziridine ring is a rate-determining step. Basic acetate such as tetramethylammonium acetate would be more suitable for this anion exchange from **2a·TfOH** to **2a·AcOH** than acetic acid. Consequently, acetic acid in **2a·AcOH** could work not only as a proton source for **2a** but also as a mild base that contributes to the deprotonation from intermediate **I** to form aziridine intermediate **II**. The triflate anion would not be sufficiently basic for this deprotonation, which would explain its lack of reactivity for the present reaction. Excess addition of acetic acid would favor the formation of **2a·AcOH** from **2a**.

In conclusion, we developed a one-pot synthesis of DAINs from the corresponding amide or thioamide. In this reaction, the additive acetic acid is suggested to act not only as a proton source but also as a base. Using this one-pot method, we were able to synthesize several DAINs having a small molecular weight without difficulty. Among them, **1c** and **1d** are of particular interest because they can be expected to contribute to extend the library of GFPc analogs. Further studies of their applications are currently in progress in our laboratory.

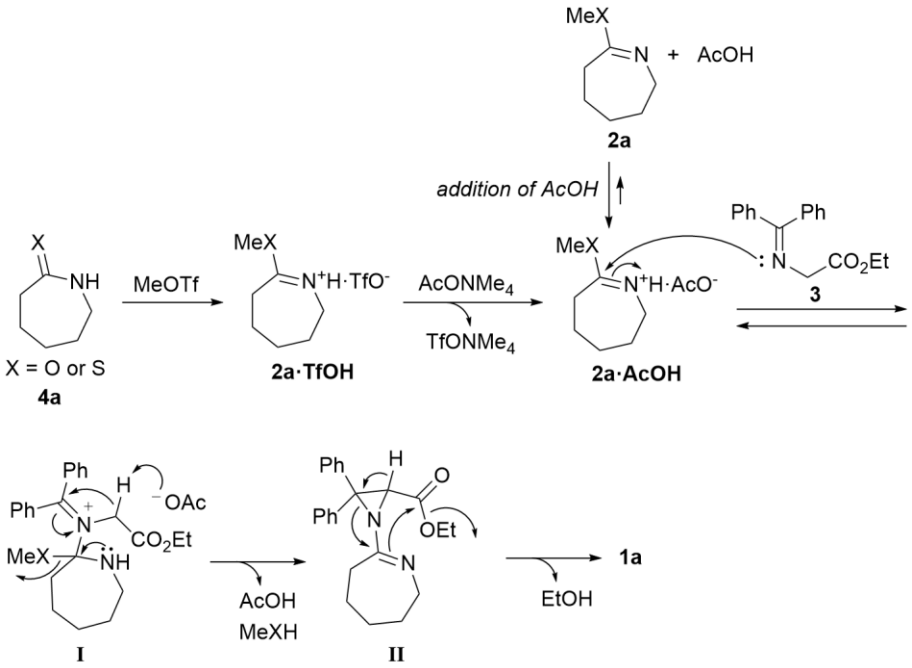


Figure 2. An improved plausible reaction mechanism from **2** to **1**

EXPERIMENTAL

General information

^{1}H- and ^{13}C-NMR spectra were recorded on a JNM-ECZ400S spectrometer at 400 and 100 MHz, respectively, and chemical shifts were reported in parts per million (ppm) relative to tetramethylsilane or the solvent signal. Mass spectra were recorded using a JEOL JMS-T100LP mass spectrometer in positive electrospray ionization (ESI) mode. Infrared (IR) spectra were recorded using a JASCO FT/IR-6600 spectrometer by attenuated total reflection (ATR). Melting points (Mp) values were measured using a Yanaco melting-point apparatus. Notably, the obtained Mp values were uncorrected. Column chromatography was performed using Fuji Silysia PSQ 100 silica gel or Teledyne Isco RediSep Rf silica gel. Compounds **4c-*S***,[13] and **4d-*O***[14] were synthesized according to literature procedures. The yields of DAINs were calculated based on the amount of MeOTf.

General procedures for the one-pot synthesis of 1:[15] synthesis of 2-(diphenylmethylene)-2,5,6,7,8,9-hexahydro-3*H*-imidazo[1,2-*a*]azepin-3-one (1a)[5]

Method A (rt): Table 2, run 4—Methyl trifluoromethanesulfonate (67 µL, 0.61 mmol) was added to a stirred solution of **4a-*O*** (103 mg, 0.91 mmol) in CH_2Cl_2 (3.0 mL) at rt, and the mixture thus obtained was stirred at rt for 24 h. Subsequently, tetramethylammonium acetate (81 mg, 0.61 mmol) was added to the mixture at rt, and the thus obtained mixture was stirred at rt for 20 min. Acetic acid (349 µL, 6.10 mmol) and glycinate **3** (815 mg, 3.05 mmol) were then added to the mixture at rt, and the resulting mixture was

stirred at rt for 48 h. Subsequent to the addition of 10% aqueous HCl and Et_2O to the mixture, the liquid layers thus obtained were shaken and separated. The organic layer was further extracted three times with 10% aqueous HCl, and the combined aqueous layer was neutralized with $NaHCO_3$ and then re-extracted twice with EtOAc. The combined EtOAc layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue thus obtained was purified by silica gel column chromatography (hexane/EtOAc = 2/1) to yield **1a** (100 mg, 52%) as a yellow solid. The ^{1}H-NMR spectrum was identical with that previously reported.[5]

Method A (reflux): Table 2, run 7—Methyl trifluoromethanesulfonate (67 µL, 0.61 mmol) was added to a stirred solution of **4a-*O*** (103 mg, 0.91 mmol) in 1,2-dichloroethane (3.0 mL) at rt, and the resulting mixture was stirred at rt for 24 h. Tetramethylammonium acetate (81 mg, 0.61 mmol) was then added to the mixture at rt, and the obtained mixture was stirred at rt for 20 min. Acetic acid (349 µL, 6.10 mmol) and glycinate **3** (815 mg, 3.05 mmol) were then added to the mixture at rt, and the mixture thus obtained was stirred under reflux conditions for 24 h. The rest of the procedure was the same as that described above, and it yielded **1a** (100 mg, 52%).

Method B—Methyl trifluoromethanesulfonate (67 µL, 0.61 mmol) was added to a stirred solution of **4a-*S*** (87 mg, 0.67 mmol) in 1,2-dichloroethane (3.0 mL) at ice-cooling temperature; the mixture was then stirred initially for 1 h at the same temperature and then for 6 h at rt. Tetramethylammonium acetate (81 mg, 0.61 mmol) was added to the mixture at rt, and the mixture thus obtained was stirred at rt for 20 min. Acetic acid (349 µL, 6.10 mmol) and glycinate **3** (815 mg, 3.05 mmol) were then added to the mixture at rt, and the resulting mixture was stirred for 24 h under reflux conditions. The rest of the procedure was the same as that described above, and it yielded **1a** (146 mg, 76%).

2-(Diphenylmethylene)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridin-3(2*H*)-one (1b)[5]

Method A (rt); reaction time for the condensation: 72 h; eluent for the silica gel column chromatography: hexane/EtOAc = 2/1; yield: 49%. *Method B*; eluent for the silica gel column chromatography: hexane/EtOAc = 2/1; yield: 49%. The ^{1}H-NMR spectrum was identical with that previously reported.[5]

5-(Diphenylmethylene)-2,3-dimethyl-3,5-dihydro-4*H*-imidazol-4-one (1c)

Method A (reflux); eluent for the silica gel column chromatography: hexane/EtOAc = 2/1 to 1/1; yield: 15%. *Method B*; reaction time for the methylation: 1 h at 0 ℃ and then 24 h at rt; eluent for the silica gel column chromatography: hexane/EtOAc = 3/2; yield: 47%. Yellow solid; Mp 131-132 ℃; IR (ATR) ν_{max}: 1703, 1619; ^{1}H-NMR ($CDCl_3$) δ: 7.56-7.54 (2H, m), 7.42-7.28 (8H, m), 3.09 (3H, s), 2.33 (3H, s); ^{13}C-NMR ($CDCl_3$) δ: 168.7, 160.6, 146.0, 139.1, 137.9, 136.1, 132.3, 130.3, 129.3, 128.8, 127.9, 127.7, 26.4, 15.5; HRMS (ESI) calcd for $C_{18}H_{17}N_2O$ $[M + H]^+$ 277.1335; found 277.1344.

3-(But-3-yn-1-yl)-5-(diphenylmethylene)-2-methyl-3,5-dihydro-4*H*-imidazol-4-one (1d)

Method A (reflux); eluent for the silica gel column chromatography: hexane/EtOAc = 2/1 to 1/1 and for PLC: CH_2Cl_2/EtOAc = 20/1; yield: 14%. *Method B*; reaction time for the methylation: 1 h at 0 ℃ and then 1 h at rt; eluent for the silica gel column chromatography: hexane/EtOAc = 2/1; yield: 41%. Yellow solid; Mp 141-142 ℃; IR (ATR) ν_{max}: 2120, 1698, 1615; ^{1}H-NMR ($CDCl_3$) δ: 7.58-7.55 (2H, m), 7.43-7.29 (8H, m), 3.68 (2H, t, J = 6.6 Hz), 2.52 (2H, td, J = 6.6, 2.7 Hz), 2.42 (3H, s), 2.01 (1H, t, J = 2.7 Hz); ^{13}C-NMR ($CDCl_3$) δ: 168.6, 160.2, 146.2, 139.1, 137.8, 135.7, 132.3, 130.4, 129.4, 128.9, 127.9, 127.8, 80.7, 70.7, 39.4, 18.5, 15.8; HRMS (ESI) calcd for $C_{21}H_{19}N_2O$ $[M + H]^+$ 315.1492; found 315.1495.

5-(Diphenylmethylene)-2-methyl-3,5-dihydro-4*H*-imidazol-4-one (1e)

Method B; eluent for the silica gel column chromatography: hexane/EtOAc = 1/2; yield: 50%. Pale yellow solid; Mp 216-217 ℃; IR (ATR) ν_{max}: 3195 (br), 1707, 1617; ^{1}H-NMR ($CDCl_3$) δ: 9.60 (1H, br s), 7.50-7.48 (2H, m), 7.41-7.28 (8H, m), 2.09 (3H, s); ^{13}C-NMR ($CDCl_3$) δ: 170.9, 159.3, 146.3, 139.3, 137.8, 136.8, 132.3, 130.6, 129.4, 128.9, 127.9, 127.8, 16.1; HRMS (ESI) calcd for $C_{17}H_{15}N_2O$ $[M + H]^+$ 263.1179; found 263.1182.

2-(Diphenylmethylene)-5,6-dihydroimidazo[2,1-*a*]isoquinolin-3(2*H*)-one (1f)[5]

Method A (reflux); eluent for the silica gel column chromatography: hexane/EtOAc = 4/1; yield: 63%. Extraction with aqueous HCl was not performed. The ^{1}H-NMR spectrum was identical with that previously reported.[5]

5-(Diphenylmethylene)-2-(4-iodophenyl)-3-methyl-3,5-dihydro-4*H*-imidazol-4-one (1g)[7]

Method B; reaction time for the anion exchange: 45 min; eluent for the silica gel column chromatography: hexane/CH_2Cl_2 = 1/2 to CH_2Cl_2; yield: 54%. Extraction with aqueous HCl was not performed. The ^{1}H-NMR spectrum was identical with that previously reported.[7]

2-(Bis(4-methoxyphenyl)methylene)-2,5,6,7,8,9-hexahydro-3*H*-imidazo[1,2-*a*]azepin-3-one (1′h)[5]

Method A (rt); eluent for the silica gel column chromatography: hexane/EtOAc = 2/1 to 1/1; yield: 51%. Ethyl 2-((bis(4-methoxyphenyl)methylene)amino)acetate[5] was used instead of **3**. Extraction with aqueous HCl was not performed. The ^{1}H-NMR spectrum was identical with that previously reported.[5]

2-(9*H*-Fluoren-9-ylidene)-2,5,6,7,8,9-hexahydro-3*H*-imidazo[1,2-*a*]azepin-3-one (1′i)[5]

Method A (rt); eluent for the silica gel column chromatography: hexane/EtOAc = 20/1 to 9/1; yield: 41%. Methyl 2-((9*H*-fluoren-9-ylidene)amino)acetate,[16] was used instead of **3**. Extraction with aqueous HCl was not performed. The ^{1}H-NMR spectrum was identical with that previously reported.[5]

(*E*)-5-(Diphenylmethylene)-3-methyl-2-styryl-3,5-dihydro-4*H*-imidazol-4-one (1j)

A mixture of **1c** (30 mg, 0.11 mmol), benzaldehyde (22 μL, 0.22 mmol), and zinc chloride (3.0 mg, 0.022 mmol) in THF (1.0 mL) was refluxed for 24 h. Subsequent to the addition of triethylamine (50 μL, 0.36

mmol), the mixture was stirred for 5 min at rt; the solvent was then evaporated under reduced pressure, and the obtained residue was purified by silica gel column chromatography (hexane/EtOAc = 3/1) to yield **1j** (32 mg, 81%) as a yellow–orange solid. Mp 180.5-182 ℃; ^{1}H-NMR ($CDCl_3$) δ: 7.97 (1H, d, J = 15.8 Hz), 7.69-7.67 (2H, m), 7.62-7.59 (2H, m), 7.44-7.32 (11H, m), 6.82 (1H, d, J = 15.8 Hz), 3.25 (3H, s); ^{13}C-NMR ($CDCl_3$) δ: 168.9, 158.2, 145.9, 140.4, 139.3, 138.3, 137.0, 135.2, 132.8, 130.5, 130.0, 129.4, 128.9, 128.8, 128.0, 127.8, 127.8, 113.0, 26.5; HRMS (ESI) calcd for $C_{25}H_{21}N_2O$ $[M + H]^+$ 365.1648; found 365.1651.

3-(2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)ethyl)-5-(diphenylmethylene)-2-methyl-3,5-dihydro-4*H*-imidazol-4-one (1k)

A mixture of **1d** (20 mg, 0.064 mmol), benzyl azide (24 µL, 0.19 mmol), *N*,*N*-diisopropylethylamine (32 µL, 0.19 mmol), and copper(I) iodide (1.8 mg, 0.0096 mmol) in THF (1.0 mL) was stirred for 16 h at rt. Subsequent to the addition of triethylamine (89 µL, 0.64 mmol), the solvent was evaporated under reduced pressure. The residue thus obtained was purified by silica gel column chromatography (hexane/EtOAc = 1/4) to yield **1k** (21 mg, 74%) as a yellow solid. Mp 121.5-123.5 ℃; ^{1}H-NMR ($CDCl_3$) δ: 7.52-7.50 (2H, m), 7.42-7.32 (9H, m), 7.27-7.20 (4H, m), 7.20 (1H, s), 5.47 (2H, s), 3.83 (2H, t, J = 7.2 Hz), 3.00 (2H, t, J = 7.2 Hz), 2.16 (3H, s); ^{13}C-NMR ($CDCl_3$) δ: 168.7, 160.4, 146.0, 144.2, 139.0, 137.8, 135.7, 134.5, 132.3, 130.4, 129.4, 129.1, 128.9, 128.7, 127.9, 127.7, 121.8, 54.1, 40.5, 24.9, 15.5; HRMS (ESI) calcd for $C_{28}H_{26}N_5O$ $[M + H]^+$ 448.2132; found 448.2129.

***N*-(But-3-yn-1-yl)ethanethioamide (4d-*S*)**

A mixture of amide **4d-*O*** (300 mg, 2.70 mmol) and Lawesson's reagent (765 mg, 1.89 mmol) in THF (30 mL) was refluxed for 2 h. After evaporation of the solvent under reduced pressure, the residue thus obtained was purified by silica gel column chromatography (hexane/EtOAc = 4/1) to yield **4d-*S*** (343 mg, 100%) as a white solid. Mp 46-48 ℃; ^{1}H-NMR ($CDCl_3$) δ: 7.50 (1H, s), 3.83 (2H, q, J = 6.1 Hz), 2.60-2.56 (2H, m), 2.59 (3H, s), 2.07 (1H, t, J = 2.5 Hz); ^{13}C-NMR ($CDCl_3$) δ: 201.6, 80.9, 70.6, 44.2, 34.3, 17.6; HRMS (ESI) calcd for $C_6H_{10}NS$ $[M + H]^+$ 128.0529; found 128.0528.

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