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A direct entry to substituted piperidinones from α,β-unsaturated amides by means of aza double Michael reaction

Kiyosei Takasu,* Naoko Nishida and Masataka Ihara*

Department of Organic Chemistry, Graduate School of Pharmaceutical Sciences, Tohoku University, Aobayama, Sendai 980-8578, Japan

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Abstract—An intermolecular aza-double Michael reaction has been developed leading to functionalized piperidin-2-ones from simple starting materials. The method allows to utilize α,β-unsaturated amides as a synthon of piperidine nucleus. The short synthesis of anti-depressant paroxetine was demonstrated by using the new methodology.

The piperidine ring system is a ubiquitous structural component of naturally occurring alkaloids, biologically active synthetic molecules, and organic fine chemicals.[1] Generally, the biological properties of piperidines are highly dependent on the type and location of substituents on the heterocyclic ring. Consequently, numerous strategies have been developed for construction of functionalized piperidines.[2] Despite this, new methodologies which rely on the use of readily available starting materials are still required for high throughput syntheses of substances in this family.

We envisioned that substituted piperidin-2-ones could be generated by coupling reactions between α,β-unsaturated amides and α,β-unsaturated esters or ketones (Fig. 1). Although α,β-unsaturated amides are commonly employed as monomers in the preparation of polymers, they have been used less often as building blocks in the synthesis of heterocyclic compounds.[3] In this regard, only a few reports exist describing how α,β-unsaturated amides serve as N–C(=O)–C–C synthons of piperidinones.[4] The potential difficulty using α,β-unsaturated amides in this manner results from its diverse reactivity. Specifically, unsaturated amides have several reactive sites, including electrophilic carbonyls and β-carbons and nucleophilic nitrogen, oxygen and α-carbon atoms. Thus, the advent of methods to control chemoselective reactions at each of these centers would add unsaturated amides to the family of versatile building blocks in synthetic organic chemistry.

Previously, we have developed a method to prepare piperidinones by intramolecular reactions of α,β-unsaturated amides possessing enoate moieties.[5] Below, we present the results of our recent studies which have uncovered an intermolecular aza-annulation process that constructs 4-, 5- and/or 6-substituted piperidin-2-ones starting with simple precursors.

Initial investigations concentrated on the reaction of *N*-benzyl-*trans*-cinnamamide (**1a**) and methyl acrylate (**2a**) (Scheme 1). When an equimolar mixture of **1a** and **2a** in 1,2-dichloroethane (DCE; 0.2 M solution of **1a**) is

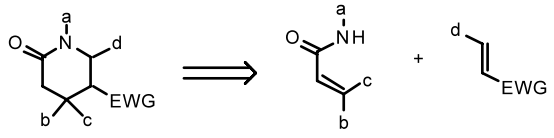
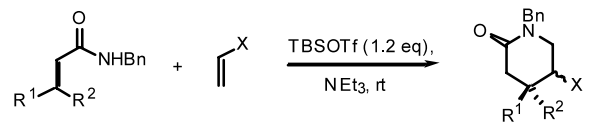


Figure 1. Our strategy for the formation of piperidin-2-ones from unsaturated amides.



1a (R^1 = Ph, R^2 = H) **2a** (X = CO_2Me) *trans*-**3a** (X; α-oriented) *cis*-**3a** (X; β-oriented)

Scheme 1.

Keywords: heterocycles; piperidines; 1,4-additions; domino reactions; unsaturated amides; anti-depressant.

* Corresponding authors. Tel.: +81-22-217-6887; fax: +81-22-217-6877; e-mail: mihara@mail.pharm.tohoku.ac.jp

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Table 1. Aza double Michael reaction of **1a** with **2a**[a]

Run	Solvent[b]	Conc. (M)	Et_3N (equiv.)	% Yield of **3a**[c]	Ratio of *trans*/*cis*[d]
1	DCE	0.2	1.5	0	–
2	DCE	0.2	0.7	37 (74)	41:59
3	DCE	0.2	0.2	0	–
4	DCE	1.0	0.7	80 (93)	53:47
5	DCM	1.0	0.7	53 (76)	49:51
6	MeCN	1.0	0.7	49 (65)	49:51
7	Toluene	1.0	0.7	29 (57)	41:59
8	Neat	—	0.7	60 (75)	40:60

[a] Reactions were performed using 1.2 equiv. TBSOTf (unpurified), 1.0 equiv. **1a**, and 1.0 equiv. **2a** at ambient temperature for 24 h.
[b] Abbreviations; DCE = 1,2-dichloroethane, DCM = dichloromethane.
[c] Conversion yields are shown in parentheses.
[d] *trans*/*cis* Ratios were determined based on isolated yields.

treated at room temperature with 1.2 equiv. of TBSOTf in the presence of 1.5 equiv. of Et_3N,[5a] the formation of piperidinone **3a** is, unfortunately, not observed. Acylate-oligomers and recovered **1a** are the only substance as observed in the crude reaction mixture (Table 1, run 1). In contrast, when 0.7 equiv. of Et_3N are used, reaction of **1a** and **2a** (under otherwise identical conditions) occurs to produce **3a** in 37% yield along with 50% of recovered **1a** (run 2). However, reaction does not take place when 0.2 equiv. of Et_3N are employed (run 3). Although we yet do not have detailed insight into the source of the phenomenon, it appears that the aza-annulation reaction is promoted by using 1.2 equiv. of TBSOTf in the presence of Et_3N within the 0.5–1.0 equiv. range.[6]

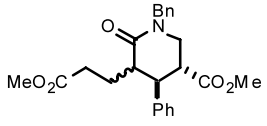
Additional studies showed that 0.7 equiv. of TMSI can be used as an alternative to TBSOTf, but the yield for production of **3a** is lower. Furthermore, we have found that substrate concentration has a significant effect upon the efficiency of this process. For example, reaction of a 1.0 M solution of **1a** and **2a** in DCE affords **3a** in 80% yield (93% conversion yield) as a ca. 1:1 mixture of diastereomers (run 4). The reaction occurs in several other solvents, such as dichloromethane and acetonitrile, but the yields are not satisfactory (runs 5–7). It is noteworthy that the annulation reaction also occurs under neat conditions to give **3a** in 60% yield (run 8). As can be seen by viewing the data in Table 1, the diastereoselectivities of all reactions are low. However, we have found that *cis*-**3a** can be smoothly converted into *trans*-**3a** by reaction with NaOMe in refluxing MeOH–toluene.[7]

These investigations led to the unexpected observation that the yield for production of piperidinone **3a** is lowered when freshly distilled TBSOTf is employed (Table 2, run 2 versus run 1).[8] In this case, 3,4,5-trisubstituted piperidin-2-one **4** is obtained in 5% yield as a mixture of diastereomers. Use of excess **2a** in the reaction promoted by the purified Lewis acid results in 48% yielding formation of **4** (run 3). We presume that **4** is generated by additional Michael reaction of double Michael intermediate **5**. In contrast, when triflic acid (the most likely impurity in non-purified TBSOTf) is present, the silyl-enolate intermediate **5** would likely undergo rapid protodesilylation rather than secondary reaction with the acrylate ester. Actually, the addition of *t*BuOH as a proton source suppresses production of the triple Michael-adduct **4** even in reactions promoted by pure TBSOTf. However, when large amounts of *t*BuOH are employed, formation of **3a** is also inhibited (run 5). Finally, 0.25 equiv. of *t*BuOH was found to be optimal, affording only **3a** in 74% yield (99% conversion yield) (run 4).

Table 2. Formation of triple Michael adduct and effect of *t*BuOH[a]

Run	*t*BuOH	% Yield[b]		
		3a (*trans*/*cis*)[c]	**4**	**1a**[d]
1[e]	0	80 (53: 47)	Trace	14
2	0	68 (53: 47)	5	17
3[f]	0	38 (nd)	48	0
4	0.25	74 (49: 51)	0	25
5	1.0	35 (51: 49)	0	56

[a] Reactions were performed using 1.2 equiv. TBSOTf (freshly distilled), 0.7 equiv. Et_3N, 1.0 equiv. **1a**, and 1.0 equiv. **2a** at ambient temperature in DCE for 24 h.
[b] Isolated yields.
[c] *trans*/*cis* Ratios were determined based on isolated yields.
[d] Recovered yields.
[e] Unpurified TBSOTf was used.
[f] 5 equiv. of **2a** was used.



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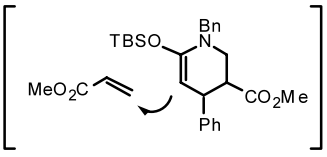

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The scope of the aza double Michael reaction was probed by using various combinations of substrates. The results of this effort, summarized in Table 3, show that α,β-unsaturated amides possessing aromatic or aliphatic substituent in the β-position participate in efficient annulations reactions with methyl acrylate (**2a**) (runs 1, 2, and 4–7). On the other hand, acrylamide (**1d**) does not undergo the desired reaction. Rather, the homo-dimeric piperidin-2-one **6** is generated in quanti-

Table 3. Formation of substituted piperidin-2-ones[a]

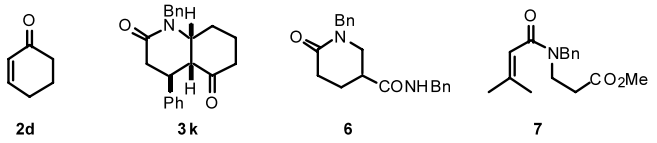
Run	**1** (R^1, R^2)	**2** (X)	Product	% yield[c]	Ratio of *trans*/*cis*[d]
1[a]	**1b** (4-MeOPh, H)	**2a** (CO_2Me)	**3b**	52 (61)	46:54
2[a]	**1c** (4-FPh, H)	**2a**	**3c**	59 (92)	51:49
3[b]	**1d** (H, H)	**2a**	**3d**	0	–
4[b]	**1e** (Me, H)	**2a**	**3e**	66 (86)	50:50
5[b]	**1f** (*i*Pr, H)	**2a**	**3f**	76 (84)	49:51
6[b]	**1g** ($(CH_2)_2OTBS$, H)	**2a**	**3g**	72 (93)	71:29
7[b]	**1h** (Me, Me)	**2a**	**3h**	88 (nd)	–
8[a]	**1a** (Ph, H)	**2b** (CO_2cHex)	**3i**	80 (88)	48:52
9[a]	**1a**	**2c** (COMe)	**3j**	32 (63)	>99:<1
10[a]	**1a**	**2d**	**3k**	51 (nd)	>99:<1

[a] Reactions were performed using 1.2 equiv. TBSOTf (freshly distilled), 0.7 equiv. Et_3N, 0.25 equiv. *t*BuOH, 1.0 equiv. **1**, and 1.0 equiv. **2** in DCE at ambient temperature for 24 h.

[b] Reactions were performed using 1.2 equiv. TBSOTf (unpurified), 0.7 equiv. Et_3N, 1.0 equiv. **1**, and 1.0 equiv. **2** in DCE at ambient temperature for 24 h.

[c] Conversion yields are shown in parentheses.

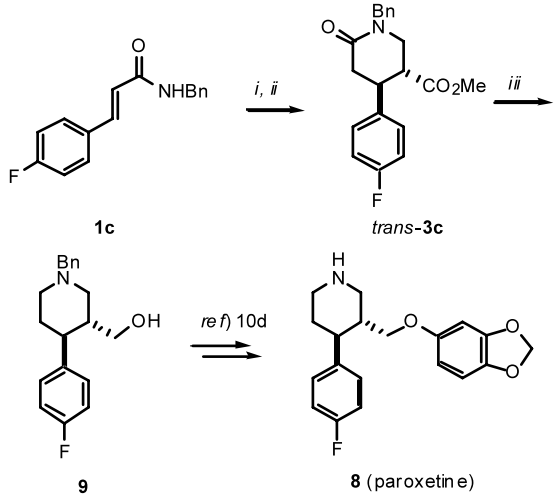
[d] *trans*/*cis* Ratios were determined based on isolated yields.



tative yield (run 3). The mono-Michael adduct **7** is formed, albeit in low yield, by reaction of β-disubstituted acrylamide **1h**. This observation suggests that the aza-annulation reaction takes place through a stepwise double Michael pathway.

The cyclohexyl acrylate (**2b**) reacts with **1a** to afford the corresponding piperidinone **3i** in good yield (run 8). Conjugated enones, such as **2c** and **2d**, also participate in the aza double Michael reaction to diastereoselectively generate the corresponding piperidies in low yields (runs 9 and 10). Interestingly, reaction of **1a** with cyclohexenone (**2d**) produces 2-quinolone **3k** as a single diastereomer in modest yield (run 10). The relative stereochemistry of **3k** was assigned by using 1D and 2D NMR methods.

To demonstrate its synthetic potential, the aza double Michael reaction was applied to the formal synthesis of paroxetine (**8**).[7,9,10] Enantiomerically pure (−)-paroxetine hydrochloride [Paxil®, Seroxat®] is a selective serotonin reuptake inhibitor (SSRI) used clinically for the treatment of depression, panic disorder, and post-traumatic stress disorder (PTSD). The sequence employed to prepare **8**, outlined in Scheme 2, begins with reaction of the unsaturated amide **1c** with acrylate **2a** in the presence of TBSOTf, Et_3N (0.7 equiv.) and *t*BuOH (0.25 equiv.) in DCE. This provides a mixture of *trans*- and *cis*-3,4-disubstituted piperidinones **3c** which without purification is treated with NaOMe to afford *trans*-**3c** in 58% overall yield (for two steps). The first annulation step can be performed under solvent-free conditions, in which case a 47% yield of *trans*-**3c** is obtained after subsequent epimerization.[11] Reduction of *trans*-**3c** with $LiAlH_4$ quantitatively furnishes the known pipereidinol **9**, whose transformation into paroxetine (**8**) has been reported by Yu.[10d] The results



Scheme 2. *Reagents and conditions*: (i) **2a** (1.0 equiv.), TBSOTf (1.2 equiv.), Et_3N (0.7 equiv.), *t*BuOH (0.25 equiv.), DCE, rt; (ii) NaOMe, MeOH–toluene, reflux (58% for two steps); (iii) $LiAlH_4$ (2 equiv.), THF, reflux (quant.).

demonstrate that the intermolecular aza double Michael reaction can be used effectively to develop new concise routes for the synthesis of functionally complex piperidines like paroxetine.

In conclusion, the studies reported above have led to the development of a novel method for facile formation of substituted piperidinones which is based on the intermolecular aza double Michael reaction. The method serves as the first general example in which α,β-unsaturated amides are used as a new class of piperidine ring synthons. In addition, we have applied the new process to a short synthesis of anti-depressant

paroxetine. Further studies are underway aimed at uncovering strategies to control the stereochemistry of the process and at determining the detailed mechanism of the reaction.

Acknowledgements

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6. **General procedures for aza-double Michael reactions**. To a mixture of **1** (1.0 equiv.), **2** (1.0 equiv.), and NEt_3 (0.7 equiv.) in 1,2-dichloroethane (1 M solution for **1**) was slowly added TBSOTf (1.2 equiv.) at ambient temperature, and then, if necessary, was added *t*BuOH (0.25 equiv.). After being stirred for 12–24 h at the same temperature, the resulting mixture was quenched by addition of satd $NaHCO_3$ and extracted with AcOEt. The organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by flash column chromatography on silica gel to afford piperidinone **3**. *trans*-**3a**; Colorless needles, mp 117–119°C; IR (KBr): ν 1734, 1645, 1497, 1439, 1257 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.34–7.16 (m, 10H), 4.74 (d, 1H, $J=14.6$ Hz), 4.55 (d, 1H, $J=14.6$ Hz), 3.52 (dd, 1H, $J=12.3$, 9.1 Hz), 3.43 (s, 3H), 3.45–3.34 (m, 2H), 3.02–2.96 (m, 1H), 2.85 (dd, 1H, $J=5.6$, 17.8 Hz), 2.68 (dd, 1H, $J=10.2$, 17.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4, 140.9, 136.5, 128.7, 128.6, 128.2, 127.5, 127.2, 126.9, 52.0, 50.0, 47.7, 46.7, 41.5, 38.0; LRMS (m/z); 323(M^+). Anal. calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.25; H, 6.52; N, 4.34. *cis*-**3a**; colorless oil; IR (neat): ν 2932, 1730, 1641, 1493, 1450, 1252, 1198, 1169, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.35–7.22 (m, 8H), 7.03–7.00 (m, 2H), 4.67 (s, 2H), 3.71 (dd, 1H, $J=12.5$, 5.1 Hz), 3.58 (s, 3H), 3.36–3.27 (m, 2H), 3.16–3.11 (m, 1H) 2.93 (d, 2H, $J=5.4$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 168.6, 139.1, 136.5, 128.5, 128.5, 128.4, 127.5, 127.3, 51.8, 50.3, 44.7, 43.8, 39.6, 36.5; LRMS (m/z); 323 (M^+). Anal. calcd for $C_{20}H_{21}NO_3 \cdot 0.25H_2O$: C, 73.26; H, 6.61; N, 4.27. Found: C, 73.12; H, 6.48; N, 4.21.
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11. In this sequence, *cis*-**3c** was obtained in 14% yield along with *trans*-**3c**. *cis*-**3c** can be converted into *trans*-**3c** by treatment with NaOMe.