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Convenient Synthesis of Substituted Piperidinones from α,β-Unsaturated Amides: Formal Synthesis of Deplancheine, Tacamonine, and Paroxetine

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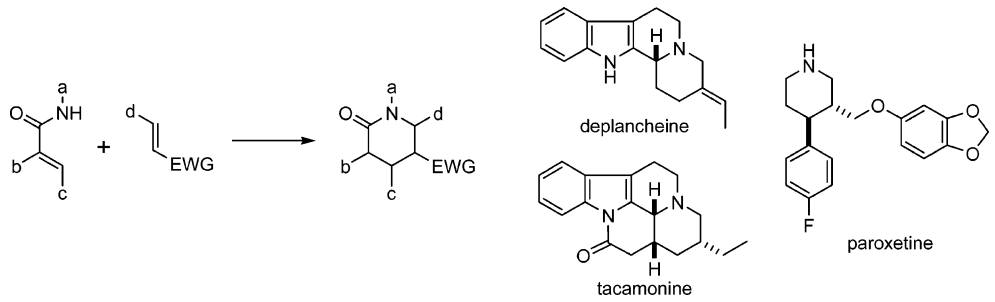


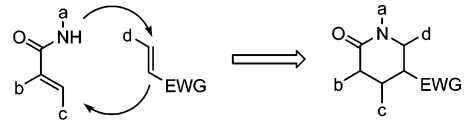
An intermolecular aza-double Michael reaction leading to functionalized piperidin-2-ones from simple starting materials has been developed. The method allows α,β-unsaturated amides to be used as a synthon of the piperidine nucleus. In addition, the utility of this methodology is demonstrated by its application to a formal synthesis of the indolo[2,3-*a*]quinolizidine alkaloids, (±)-deplancheine, (±)-tacamonine, and the antidepressant paroxetine.

Introduction

A piperidine ring is a ubiquitous molecular skeleton, which appears in naturally occurring substances as well as synthetic biologically active molecules.[1] It is widely accepted that the biological properties of piperidines are highly dependent on the type and location of substituents on the heterocyclic ring. Accordingly, great attention has been paid to the construction of functionalized piperidine compounds.[2] It is well-documented that piperidin-2-ones are common synthetic precursors for biologically important polycyclic alkaloids, such as indolo[2,3-*a*]quinolizidines and benzo[*a*]quinolizidines.

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 (Scheme 1). α,β-Unsaturated carbonyl compounds comprise one of the most important families of organic

SCHEME 1



substances. Conjugate addition and Diels−Alder reactions of members of this family, including enones, enals, and enoates, have been utilized often in the total synthesis of naturally occurring substances.[3] In addition, much attention has been given to these substances in the context of formation of fundamentally important materials in polymer chemistry. Although α,β-unsaturated amides are commonly employed as monomers in the preparation of polymers, less attention has been given to their use as building blocks in the synthesis of heterocyclic compounds.[4] In this regard, only a few reports exist describing how α,β-unsaturated amides serve as N−C(=O)−C−C synthons of piperidinones.[5,6]

(1) (a) Elbein, D. A.; Molyneux, R. In *Alkaloids*; *Chemical and Biological Perspectives*; Palletier, S. W., Ed.; John Wiley & Son: New York, 1987; Vol. 57. (b) O'Hagan, D. *Nat. Prod. Rep*. **2000**, *17*, 435−446.

(2) (a) Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781−1813. (b) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953−2989 (c) Buffat, M. G. P. *Tetrahedron* **2004**, *69*, 1701−1729 and references therein.

(3) (a) Carruthers, W. In *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press: Oxford, UK, 1990. (b) Kobayashi, S.; Jørgensen, K. A., Eds. *Cycloaddition Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2002. (c) Boger, D. L.; Weinreb, S. M. *Hetero Diels−Alder Methodology in Organic Synthesis*; Academic Press: San Diego, CA, 1987. (d) Jayakumar, S.; Ishar, M. P. S.; Mahajan, M. P. *Tetrahedron* **2002**, *58*, 379−471.

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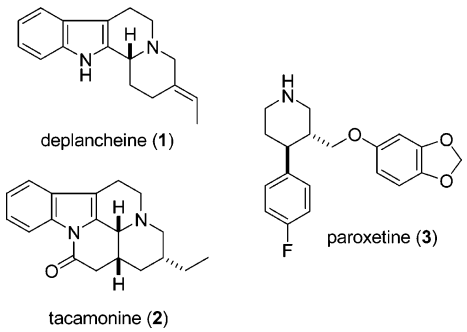
CHART 1

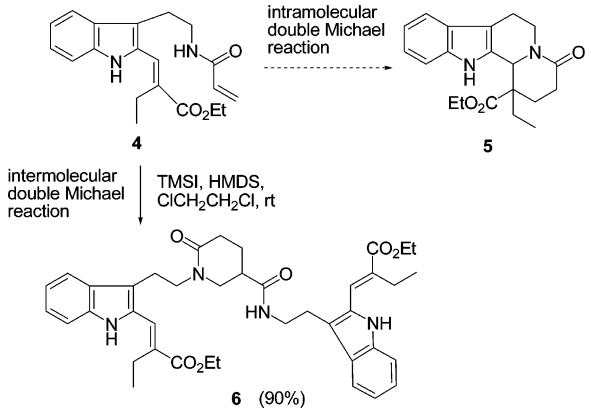


The potential difficulty of using α,β-unsaturated amides in this manner results from their diverse reactivity. Specifically, unsaturated amides have several reactive sites, including electrophilic carbonyls and β-carbons and nucleophilc nitrogen, oxygen, and α-carbon atoms. Thus, the advent of methods to control chemoselective reactions at each of these centers would add unsaturated amides to the family of versatile building blocks in synthetic organic chemistry. In this paper, we describe a new and facile strategy to form multi-substituted piperidin-2-ones from α,β-unsaturated amides by means of the intermolecular aza-double Michael reaction, and its synthetic application toward (±)-deplancheine (**1**), (±)-tacamonine (**2**), and paroxetine (**3**).[7]

Results and Discussion

Intermolecular Aza-Double Michael Reaction (Homocycloaddition Reaction). Previously, we have described a new process, termed the intramolecular aza-double Michael reaction, that transforms α,β-unsaturated amide tethered α,β-unsaturated esters to 5-alkoxycarbonylpiperidin-2-ones.[8] In the course of our investigation, we observed that reaction of the substituted acrylamide **4** with trimethylsilyl iodide (TMSI) in the presence of hexamethyldisilazane (HMDS) in 1,2-dichloroethane (DCE) did not yield the intramolecular adduct **5**. Rather, the intermolecular dimeric adduct **6** was produced in high yield under these conditions (Scheme 2). When other Lewis acids and/or amine bases were used, only complicated mixtures of products including acrylamide oligomers were generated.

SCHEME 2



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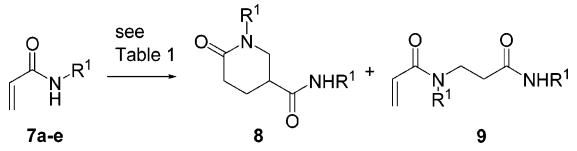


TABLE 1. Homocycloaddition of 7 by Means of Intermolecular Aza-Double Michael Reaction

				yield (%)	
entry	**7** (R^1)	conditions[a]	solvent	**8**	**9**
1	**7a** (Bn)	A	DCM	86	0
2	**7a**	B	DCM	80	0
3	**7b** (cyclohexyl)	B	DCM	78	0
4	**7c** (2-indolylethyl)	B	DCM	56	0
5	**7c**	B	DCE	90	0
6	**7d** (2-phenylethyl)	B	DCE	94	0
7	**7e** (Ph)	B	DCE	0	0
8	**7e**	A	DCE	10	18

[a] Conditions A: Reactions were carried out with 1.2 equiv of TMSI and 1.5 equiv of HMDS in 0.2 M solution at ambient temperature for 2 h. Conditions B: Reactions were carried out with 1.2 equiv of TBSOTf and 1.5 equiv of NEt_3 in 0.2 M solution at ambient temperature for 2 h.

First, we considered that the acrylamide cyclodimerization reaction would serve as a new method for the formation of 5-carbamoylpiperidin-2-ones (Scheme 3). Studies with several *N*-monosubstituted acrylamides **7a**−**e** have demonstrated the validity of this proposal (Table 1). The procedure used for these reactions is exemplified by reaction of *N*-benzylacrylamide **7a**. To a 0.2 M solution of **7a** and HMDS (1.5 equiv) in dichloromethane (DCM) is added TMSI (1.2 equiv) and the resulting mixture was stirred at ambient temperature for 2 h. Workup followed by chromatography on silica gel furnished the piperidinone **8a** in 86% yield (entry 1). The reaction of **7a** promoted by using *tert*-butyldimethylsilyl triflate (TBSOTf) and triethylamine also afforded **8a** in a high yield (entry 2). Because of its better stability and ease of handling, TBSOTf-NEt_3, rather than TMSI-HMDS, was used for the reactions of acrylamides **7b**−**d** to give 5-substituted piperidinones **8b**−**d** in high yields (entries 3−6). When DCE was used as a solvent, the reaction yield was significantly enhanced (entry 4 versus 5). On the contrary, reaction of *N*-phenylacrylamide (**7e**) afforded no desired piperidinone **8e** under the TBSOTf-

(4) Cycloaddition reactions of α,β-unsaturated imines, which are monoreduced derivertives of α,β-unsaturated amides, are well investigated: (a) Boger, D. L.; Weinreb, S. M. *Hetero Diels−Alder Methodology in Organic Synthesis*; Academic Press: San Diego, CA, 1987; pp 240−255. (b) Jayakumar, S.; Ishar, M. P. S.; Mahajan, M. P. *Tetrahedron* **2002**, *58*, 379−471. (c) Wei, L.-L.; Hsung, R. P.; Sklenicka, H. M.; Gerasyuto, A. I. *Angew. Chem., Int. Ed.* **2001**, *40*, 1516−1518.

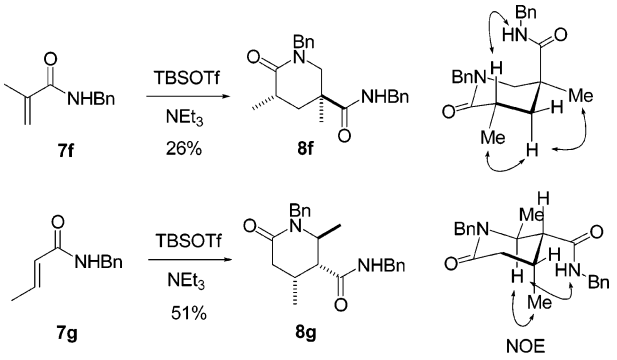
(5) To our best knowledge, only limited examples were reported for the synthesis of piperidines by means of cyclodimerization of acrylamide equivalents: (a) Lorente, A.; Navio, J. L. G.; Perez, J. C. L.; Soto, J. L. *Synthesis* **1985**, 89−92. (b) Elliott, M. C.; Galea, N. M.; Long, M. S.; Willock, D. J. *Tetrahedron Lett.* **2001**, *42*, 4937−4939. (c) Dietz, G.; Fielder, W.; Faust, G. *Chem. Ber.* **1967**, *100*, 3127−3134. (d) O'Callagham, C. N.; McMurry, T. B. H.; Cardin, C. J.; Wilcock, D. J. *J. Chem. Res.* (*S*) **1994**, 401−427.

(6) Our recent examples for the use of α,β-unsaturated amides as a piperidine synthon: (a) Takasu, K.; Nishida, N.; Ihara, M. *Synlett* **2004**, 1844−1846. (b) Takasu, K.; Nishida, N.; Ihara, M. *Synthesis* **2004**, 2222−2225.

(7) A part of this work was published as a preliminary communication: Takasu, K.; Nishida, N.; Ihara, M. *Tetrahedron Lett.* **2003**, *44*, 7429−7432.

(8) (a) Ihara, M.; Ishida, Y.; Tokunaga, Y.; Kabuto, C.; Fukumoto, K. *J. Chem. Soc., Chem. Commun.* **1995**, 2085−2086. (b) Suzuki, M.; Ihara, M. *Heterocycles* **2000**, *52*, 1083−1084. (c) Mekouar, K.; Genisson, Y.; Leue, S.; Greene, A. E. *J. Org. Chem.* **2000**, *65*, 5212−5215.

SCHEME 4

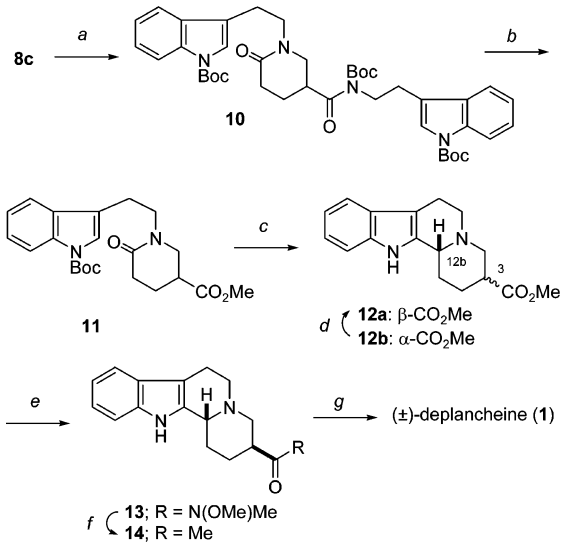


NEt_3 conditions (entry 7). It is noteworthy that the reaction of **7e** with TMSI-HMDS gave the mono-Michael adduct **9e** along with cycloadduct **8e** (entry 8). This observation suggests that the piperidinone **8e** is formed through a stepwise double Michael pathway via the intermediacy of **9e**.

The homocycloaddition is applicable to both α- or β-substituted α,β-unsaturated amides (Scheme 4). Although the processes require further optimization, reactions of methacrylamide **7f** and crotonamide **7g** proceeded to furnish multi-substituted piperidinones **8f** and **8g** in 26% and 51% yields, respectively. Interestingly, both adducts were obtained as single diastereomers. The structures and stereochemistries of **8f** and **8g** were firmly established by using 1D and 2D NMR as well as NOE methods.

Formal Synthesis of (±)-Deplancheine and (±)-Tacamonine. The products of these reactions, e.g., **8c** and **8d**, are expected to be potentially useful intermediates in the synthesis of piperidine alkaloids. Owing to this, our attention was next directed at the formal synthesis of indole alkaloids (±)-deplancheine (**1**)[9,10] and (±)-tacamonine (**2**)[11,12] starting with **8c**. (+)-Deplancheine, having an unusual Corynantheine-type structure, was isolated from the New Caledonian plant *Alstonia deplanchei*.[9] Tacamonine, one of the takamane-type alkaloids, was isolated from *Tabersonaemontana eglandulosa*.[11] Natural tacamonine displays vasodilator and hypertensive activity. Recently, it has been found by us that the synthetic (±)-tacamonine shows a selective inhibitory effect against muscarine M2 receptor.[12d] Several groups have reported racemic and asymmetric total syntheses of the targets.[10,12]

SCHEME 5. Formal Synthesis of (±)-Deplancheine[a]



[a] Reagents and conditions: (a) Boc_2O, DMAP, NEt_3 (96%); (b) NaOMe (86%); (c) (i) $POCl_3$, (ii) $NaBH_4$ (**12a**; 55%, **12b**; 26%); (d) TFA, reflux (43%); (e) for **12a**, MeONHMe·HCl, $AlMe_3$ (92%); (f) MeMgBr (50%); (g) see ref 10d.

The route used for the formal synthesis of deplancheine (**1**) is shown in Scheme 5. The tri-Boc derivative **10** was formed from **8c** in 96% yield and then treated with sodium methoxide to give methyl ester **11** in 86% yield along with Boc-tryptamine.[13] Bischler−Napieralski reaction of **11** with $POCl_3$ in acetonitrile, followed by $NaBH_4$ reduction, afforded a diastereomeric mixture of **12a** and **12b** in respective yields of 55% and 26%. The stereochemistries of **12a** and **12b** were assigned by comparison of their spectral data with those reported previously.[14] In addition, **12b** could be converted to the desired diastereomer **12a** by stirring at reflux in TFA.[15] The Boc group at the nitrogen atom of indole in **11** was lost under the conditions used for Bischler−Napieralski cyclization. Treatment of **12a** with methoxymethylamine hydrochloride in the presence of $AlMe_3$ furnished the Weinreb amide **13** in 92% yield. Then, **13** was subjected to Grignard addition to give the known ketone **14** in 50% yield, which had been converted into (±)-deplancheine (**1**) by Pakrashi and co-workers.[10d] Spectral data for the synthetic compound **14** were identical with those reported in the literature.[10d]

Formal synthesis of tacamonine (**2**) was achieved from **11** as shown in Scheme 6. Selective reduction of ester **11** by treatment with $LiBH_4$, followed by acidic treatment, afforded the known alcohol **15** in good yield. Conversion of alcohol **15** into **2** has been previously reported.[12c]

Intermolecular Aza-Double Michael Reaction (Heterocycloaddition Reaction). We have demonstrated the direct entry to a functionalized piperidinone by way of the aza-double Michael reaction between the same two α,β-unsaturated amides (homocoupling reaction) as above. However, the reaction is still less atom-

(9) Besseliévre, R.; Cosson, J.-P.; Das, B. C.; Husson, H.-P. *Tetrahedron Lett.* **1980**, *21*, 63−66.

(10) (a) Ashcroft, W. R.; Joule, J. A. *Tetrahedron Lett.* **1980**, *21*, 2341−2344. (b) Calabi, L.; Danieli, B.; Lesma, G.; Palmisano, G. *Tetrahedron Lett.* **1982**, *23*, 2139−2142. (c) Rosenmund, P.; Casutt, M. *Tetrahedron Lett.* **1983**, *24*, 1771−1774. (d) Mandal, S. B.; Pakrashi, S. C. *Heterocycles* **1987**, *26*, 1557−1562. (e) Itoh, T.; Matsuya, Y.; Enomoto, Y.; Ohsawa, A. *Heterocycles* **2001**, *55*, 1165−1171. (f) Meyers, A. I.; Sohda, T.; Loewe, M. F. *J. Org. Chem.* **1986**, *51*, 3108−3112.

(11) Van Beek, T. A.; Verpoorte, R.; Lankhorst, P. P.; Svendsen, A. B. *Tetrahedron* **1984**, *40*, 737−748.

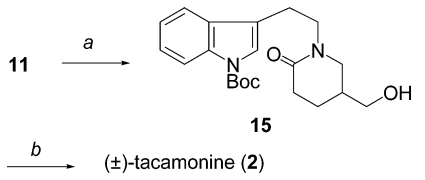
(12) (a) Ihara, M.; Setsu, F.; Shohda, M.; Taniguchi, N.; Fukumoto, K. *J. Org. Chem.* **1994**, *59*, 5317−5323. (b) Lounasmaa, M.; Karinen, K.; Din Belle, D.; Tolvanen, A. *Tetrahedron* **1998**, *54*, 157−164. (c) Danieli, B.; Lesma, G.; Macecchini, S.; Passarella, D.; Silvani, A. *Tetrahedron*: *Asymmetry* **1999**, *10*, 4057−4064. (d) Suziki, M.; Ihara, M. *Heterocycles* **2000**, *52*, 1083−1085. (e) Ho, T.-L.; Gorbets, E. *Tetrahedron* **2002**, *58*, 4969−4973. (f) Chen, C.-Y.; Chang, M.-Y.; Hsu, R.-T.; Chen, S.-T.; Chang, N.-C. *Tetrahedron Lett.* **2003**, *44*, 8627−8630.

(13) Flynn, D. L.; Zelle, R. E.; Grieco, P. A. *J. Org. Chem.* **1983**, *48*, 2424−2426.

(14) Lounasmaa, M.; Hämeilä, M. *Tetrahedron* **1978**, *34*, 437−442.

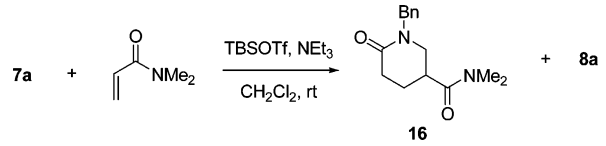
(15) Lounasmaa, M.; Berner, M.; Brunner, M.; Suomalainen, H.; Tolvanen, A. *Tetrahedron* **1998**, *54*, 10205−10216.

SCHEME 6. Formal Synthesis of (±)-Tacamonine[a]



[a] Reagents and conditions: (a) $LiBH_4$; H^+; (b) see ref 12c.

SCHEME 7



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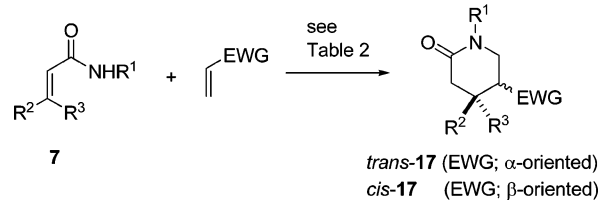


economic because the product has the same substituents on the nitrogen atom of both amide functions. Next, we examined the heterocycloaddition reaction between an α,β-unsaturated amide and another α,β-unsaturated carbonyl compound as the coupling partner. Despite our considerable efforts using acrylamide **7a** as a substrate, no heterocoupling adduct but the formation of homodimer **8a** was observed with use of a variety of activated olefins, such as α,β-unsaturated ketones, aldehydes, and esters, under the above conditions. When **7a** was treated with *N,N*-dimethylacrylamide, a small amount of heterodimer **16** (~30% yield) was produced along with homodimer **8a** (Scheme 7). The observation indicates that the acrylamide itself is more reactive as a Michael acceptor rather than the other activated olefins in our reaction system. Consequently, control of the reactivity at the β-position of unsaturated amide should be crucial for the heterocycloaddition reaction. Thus, we considered that installation of a bulky β-subsitutent would suppress the undesired homocycloaddition reaction.

When an equimolar mixture of *N*-benzyl-*trans*-cinnamamide (**7h**) and methyl acrylate in DCE (0.2 M solution of **7h**) was treated at ambient temperature with 1.2 equiv of TBSOTf in the presence of 1.5 equiv of NEt_3 (the same conditions as the above homocycloaddition reaction), neither homo- nor heterocoupling adducts were obtained (Scheme 8 and Table 2, entry 1). Acrylate-oligomers and recovered **7h** were the only substances observed in the crude reaction mixture. In contrast, when 0.7 equiv of NEt_3 was used, reaction of **7h** and methyl acrylate produced **17h** in 37% yield along with 50% of recovered **7h** (entry 2). However, no reaction took place when 0.2 equiv of NEt_3 was employed (entry 3). Although we do not have detailed insight into the source of the phenomenon, it appears that the heterocycloaddition is promoted by using 1.2 equiv of TBSOTf in the presence of NEt_3 within the 0.5−1.0 equiv range.

TABLE 2. Aza-Double Michael Reaction of 7h (R^1 = Bn, R^2 = Ph, R^3 = H) with Methyl Acrylate[a]

entry	solvent	concn (M)	NEt_3 (equiv)	% yield of **17h**[b]	ratio of trans/cis[c]
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 with 1.2 equiv of TBSOTf (unpurified), 1.0 equiv of **7h**, and 1.0 equiv of acrylate at ambient temperature for 24 h. [b] Conversion yields are shown in parentheses. [c] Trans/cis ratios were determined based on isolated yields.

TABLE 3. Formation of Triple Michael Adduct and Effect of *t*BuOH[a]

		% yield[b]		
entry	*t*BuOH	**17h** (trans/cis)[c]	**18**	**7h**[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 with 1.2 equiv of TBSOTf (freshly distilled), 0.7 equiv of NEt_3, 1.0 equiv of **7h**, and 1.0 equiv of acrylate 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 acrylate was used.

Additional studies showed that 0.7 equiv of TMSI could be used as an alternative to TBSOTf, but the yield for production of **17h** was 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 **7h** in DCE afforded **17h** in 80% yield (93% conversion yield) as a ca. 1:1 mixture of diastereomers (entry 4). The reaction occurred in several other solvents, such as DCM and acetonitrile, but the yields were not satisfactory (entries 5−7). It is noteworthy that the cycloaddition reaction also occurred under neat conditions to give **17h** in 60% yield (entry 8). As can be seen by viewing the data in Table 2, the diastereoselectivities of all reactions were low. However, we have found that *cis*-**17h** could be smoothly converted into *trans*-**17h** by reaction with NaOMe in refluxing MeOH−toluene.[16]

These investigations led to the unexpected observation that the yield for production of piperidinone **17h** was lowered when freshly distilled TBSOTf was employed (Table 3, entry 2 versus 1).[17] In this case, 3,4,5-trisubstituted piperidin-2-one **18** was obtained in 5% yield as a mixture of diastereomers. Use of excess acrylate in the reaction promoted by the purified Lewis acid resulted in 48% yield of **18** (entry 3). We presume that compound

(16) Sugi, K.; Itaya, N.; Katsura, T.; Igi, M.; Yamazaki, S.; Ishibashi, T.; Yamaoka, T.; Kawada, Y.; Tagami, Y.; Otsuki, M.; Ohshima, T. *Chem. Pharm. Bull.* **2000**, *48*, 529−536.

(17) Reactions with unpurified R_3SiX sometimes gave different results (for **17a**; 60−80% yield), whereas use of freshly distilled TBSOTf with *t*BuOH (0.25 equiv) afforded highly reproducible results. We have reported that the purity of TMSI affects the chemical yield of intramolecular Michael-aldol reactions. Takasu, K.; Ueno, M.; Ihara, M. *J. Org. Chem.* **2001**, *66*, 4667−4672.

TABLE 4. Formation of Substituted Piperidin-2-ones[a]

entry	amide (R^1, R^2, R^3)	activated olefin	product	% yield[c]	trans/cis[d]
1[a]	**7i** (Bn, 4-MeOPh, H)	methyl acrylate	**17i**	52 (61)	46:54
2[a]	**7j** (Bn, 4-FPh, H)	methyl acrylate	**17j**	59 (92)	51:49
3[b]	**7a** (Bn, H, H)	methyl acrylate	**17a**	0	
4[b]	**7g** (Bn, Me, H)	methyl acrylate	**17g**	66 (86)	50:50
5[b]	**7k** (*i*Pr, H, Bn)	methyl acrylate	**17k**	76 (84)	49:51
6[b]	**7*l*** (Bn, $(CH_2)_2$OTBS, H)	methyl acrylate	**17*l***	72 (93)	71:29
7[b]	**7m** (Bn, Me, Me)	methyl acrylate	**17m**	88	
8[b]	**7n** (Bn, $-(CH_2)_5-$)	methyl acrylate	**17n**	85	
9[a]	**7o** (see Chart 2)	methyl acrylate	**17o**	48 (87)	48:52
10	**7p** (see Chart 2)	methyl acrylate	**17p**	52 (79)	52:48
11[a]	**7h** (Bn, Ph, H)	cyclohexyl acrylate	**17q**	80 (88)	48:52
12[a]	**7h**	methyl vinyl ketone	**17r**	32 (63)	>99:<1
13[a]	**7h**	2-cyclohexenone	**17s**	51	>99:<1

[a] Reactions were performed with 1.2 equiv of TBSOTf (freshly distilled), 0.7 equiv of NEt_3, 0.25 equiv of *t*BuOH, 1.0 equiv of **7**, and 1.0 equiv of acrylate (or enone) in DCE at ambient temperature for 24 h. [b] Reactions were performed with 1.2 equiv of TBSOTf (unpurified), 0.7 equiv of NEt_3, 1.0 equiv of **7**, and 1.0 equiv of acrylate (or enone) 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.

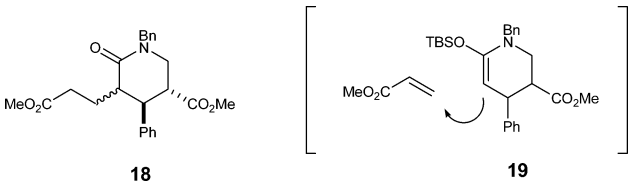


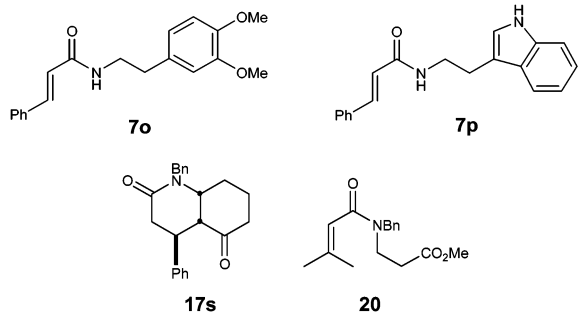
FIGURE 1. Formation of triple Michael adduct

18 is generated by additional Michael reaction of double Michael intermediate **19** (Figure 1). In contrast, when triflic acid (the most likely impurity in nonpurified TBSOTf) was present, the silyl enol ether intermediate **19** would likely undergo rapid protodesilylation rather than secondary reaction with the acrylic ester. Actually, the addition of *t*BuOH as a proton source suppressed production of the triple Michael-adduct **18** even in reactions promoted by pure TBSOTf. However, when large amounts of *t*BuOH were employed, formation of **17h** was also inhibited (entry 5). Finally, 0.25 equiv of *t*BuOH was found to be optimal, affording only **17h** in 74% yield (99% conversion yield) (entry 4).

The scope of the aza-double Michael reaction was probed by using various combinations of substrates (Table 4). The results of this effort show that α,*β*-unsaturated amides possessing aromatic or aliphatic substituents at the *β*-position participate in efficient cycloaddition reactions with methyl acrylate (entries 1, 2, and 4−10). The heterocycloaddition reaction of acrylamide **7a** did not undergo the desired reaction under even the newly optimized conditions and gave homodimer **8a** (entries 3). In the reaction of crotonamide **7g** with methyl acrylate, homodimer **8g** was produced in ∼10% yield along with heterodimer **17g** (66% yield, entry 4). In contrast, *β*-disubstituted acryl amides, such as **7m** and **7n**, afforded the desired heterodimers in a higher yield (entries 7 and 8).Mono-Michael adduct **20** was formed, albeit in low yield, by reaction of *β*-disubstituted acrylamide **7m**. This observation suggests that the heterocycloaddition reaction takes place through a stepwise double Michael pathway.

Cyclohexyl acrylate reacted with **7h** to afford the corresponding piperidinone **17q** in good yield (entry 11). Conjugated enones, such as methyl vinyl ketone (MVK) and 2-cyclohexenone, also participated in the aza-double Michael reaction to diastereoselectively generate the corresponding piperidinones (entries 12 and 13). Interestingly, reaction of **7h** with cyclohexenone produced 2-quinolone **17s** as a single diastereomer in modest yield (entry 13). The relative stereochemistry of **17s** was assigned by using 1D and 2D NMR methods.

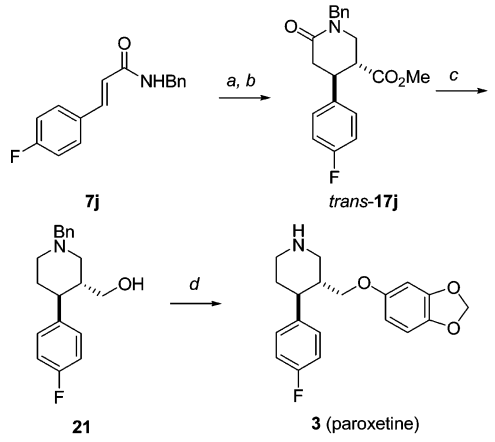
CHART 2



Formal Synthesis of Paroxetine. To demonstrate its synthetic potential, the aza-double Michael reaction was applied to the formal synthesis of paroxetine (**3**).[16,18,19] 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 **3**, outlined in Scheme 9, started with reaction of the unsaturated amide **7j** with methyl acrylate in the presence of TBSOTf (1.2 equiv), NEt_3 (0.7 equiv), and *t*BuOH (0.25 equiv) in DCE. This provided a mixture of *trans*- and *cis*-3,4-disubstituted piperidinones **17j**, which without purification was treated with NaOMe to afford *trans*-**17j** in 58% overall yield (for 2 steps). The first cycloaddition step could be performed under solvent-free conditions, in which case a 47% yield of *trans*-**17j** was obtained after subsequent epimeriza-

(18) Dechant, K. L.; Clissold, S. P. *Drugs* **1991**, *41*, 225−253.
(19) Recent examples for the synthesis of paroxetine, see: (a) Greenhalgh, D. A.; Simpkins, N. S. *Synlett* **2002**, 2074−2076. (b) Senda, T.; Ogasawara, M.; Hayashi, T. *J. Org. Chem.* **2001**, *66*, 6852−6856. (c) Cossy, J.; Mirguet, O.; Pardo, D. G.; Desmurs, J.-R. *Eur. J. Org. Chem.* **2002**, 3543−3551. (d) Yu, M. S.; Lantos, I.; Peng, Z.-Q.; Yu, J.; Cacchio, T. *Tetrahedron Lett.* **2000**, *41*, 5647−5651. (e) Murthy, K. S. K.; Rey, A. W.; Tjepkema, M. *Tetrahedron Lett.* **2003**, *44*, 5355−5358. (f) Chen, C.-Y.; Chang, B.-R.; Tsai, M.-R.; Chang, M.-Y.; Chang, N.-C. *Tetrahedron* **2003**, *59*, 9383−9387. (g) Igarashi, J.; Ishikawa, H.; Kobayashi, Y. *Tetrahedron Lett.* **2004**, *45*, 8065−8068. (h) Laszlo, C.; Nemes, A.; Seboek, F.; Szantay, C., Jr.; Mak, M. *Eur. J. Org. Chem.* **2004**, 3336−3339.

SCHEME 9. Formal Synthesis of Paroxetine[a]



[a] Reagents and conditions: (a) TBSOTf (1.2 equiv), NEt_3 (0.7 equiv), *t*BuOH (0.25 equiv), DCE, rt; (b) NaOMe, MeOH−toluene, reflux (58% for 2 steps); (c) $LiAlH_4$ (2 equiv), THF, reflux (quant); (d) see ref 19d.

tion.[20] Reduction of *trans*-**17j** with $LiAlH_4$ quantitatively furnished the known pipereidinol **21**, whose transformation into paroxetine (**3**) has been reported.[19d] The results demonstrate that the intermolecular aza-double Michael reaction can be used effectively to develop new concise routes for the synthesis of functionally complex piperidines such as paroxetine.

Conclusions

In conclusion, the studies reported above have led to the development of a novel method for facile formation of substituted piperidinones from simple α,β-unsaturated amides by means of the intermolecular aza-double Michael reaction. The new strategy should have broad applications to the synthesis of alkaloids as well as medicinally important heterocyclic compounds. A demonstration of the potential of homocycloaddition reaction is found in the formal racemic synthesis of two natural indole alkaloids, deplancheine and tacamonine. In addition, we have applied the heterocycloaddition reaction to a short synthesis of the antidepressant 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.

Experimental Section

General Procedure for the Homocycloaddition Reaction (Schemes 2−4). To a solution of acrylamide **7** (1.0 equiv) and triethylamine (1.5 equiv) in 1,2-dichloroethane (0.2 M solution) was added TBSOTf (1.2 equiv) at ambient temperature. After being stirred for 2 h and quenched with aqueous $NaHCO_3$, the mixture was extracted with AcOEt. The organic layer was washed with brine, dried, and concentrated. The resulting residue was chromatographed on silica gel (AcOEt) to afford piperidinone **8**.

1-Benzyl-5-(*N*-benzylcarbamoyl)piperidin-2-one (8a): colorless oil; IR (neat) ν 3288, 3068, 2932, 1633, 1555 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34−7.18 (m, 10H), 6.25 (br s, 1H), 4.64 (d, 1H, J = 14.7 Hz), 4.44 (d, 1H, J = 14.7 Hz), 4.42−4.27 (m, 2H), 3.48 (dd, 1H, J = 12.2, 10.2 Hz), 3.31 (dd, 1H, J = 12.2, 5.2 Hz), 2.62−2.48 (m, 2H), 2.41−2.30 (m, 1H), 2.03−1.96 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 169.0, 138.0, 136.7, 128.7, 128.1, 127.7, 127.6, 50.1, 48.6, 43.4, 40.8, 30.9, 24.9; LRMS *m/z* 322 (M^+); HRMS calcd for $C_{20}H_{22}N_2O_2$ 322.1681, found 322.1676.

(3*S,5*S**)-1-Benzyl-5-(*N*-benzylcarbamoyl)-3,5-dimethylpiperidin-2-one (8f):** colorless oil; IR (neat) ν 3330, 2931, 1627 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30−7.20 (m, 8H), 7.06 (d, 2H, J = 8.0 Hz), 5.54 (br s, 1H), 5.04 (d, 1H, J = 14.2 Hz), 4.27 (dd, 1H, J = 14.8, 5.8 Hz), 4.12 (dd, 1H, J = 14.8, 5.8 Hz), 4.05 (d, 1H, J = 14.2 Hz), 3.47 (dd, 1H, J = 13.2, 2.6 Hz), 3.13 (d, 1H, J = 13.2 Hz), 2.45−2.40 (m, 1H), 2.32 (ddd, 1H, J = 13.2, 6.2, 2.6 Hz), 1.47 (t, 1H, J = 13.2 Hz), 1.24 (d, 3H, J = 7.0 Hz), 1.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 172.5, 138.0, 136.8, 128.8, 128.7, 127.9, 127.55, 127.49, 54.1, 50.2, 43.6, 42.0, 40.8, 34.2, 25.2, 17.4; LRMS *m/z* 350 (M^+); HRMS calcd for $C_{22}H_{26}N_2O_2$ 350.1994, found 350.1989.

(3*R,4*R**,5*S**)-1-Benzyl-5-(*N*-benzylcarbamoyl)-4,6-dimethylpiperidin-2-one (8g):** colorless oil; IR (neat) ν 3280, 3067, 2931, 1648, 1540 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30−7.21 (m, 8H), 7.16 (d, 2H, J = 6.0 Hz), 5.72 (s, 1H), 5.34 (d, 1H, J = 15.2 Hz), 4.30 (dd, 1H, J = 14.8, 6.0 Hz), 4.20 (dd, 1H, J = 14.8, 6.0 Hz), 3.99 (d, 1H, J = 15.2 Hz), 3.73−3.69 (m, 1H), 2.54−2.42 (m, 2H), 2.34−2.31 (m, 2H), 1.23 (d, 3H, J = 6.4 Hz), 1.01 (d, 3H, J = 6.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 169.3, 138.1, 137.2, 128.7, 128.6, 128.2, 127.7, 127.5, 127.4, 51.7, 51.3, 46.9, 43.4, 38.3, 27.3, 20.3, 16.9; LRMS *m/z* 350 (M^+); HRMS calcd for $C_{22}H_{26}N_2O_2$ 350.1994, found 350.2002.

General Procedures for the Heterocycloaddition Reaction (Scheme 8). To a mixture of **7** (1.0 equiv), acrylate (1.0 equiv), and NEt_3 (0.7 equiv) in 1,2-dichloroethane (1 M solution for **7**) was slowly added TBSOTf (1.2 equiv) at ambient temperature, and then *t*BuOH (0.25 equiv) was added. After being stirred for 12−24 h at the same temperature, the resulting mixture was quenched by addition of saturated $NaHCO_3$ 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 **17**.

(4*S,5*R**)-1-Benzyl-5-(methoxycarbonyl)-4-phenylpiperidin-2-one (*trans*-17h):** colorless needles, mp 117−119 °C (from AcOEt−hexane); 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 171.9, 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.

(4*S,5*S**)-1-Benzyl-5-(methoxycarbonyl)-4-phenylpiperidin-2-one (*cis*-17h):** 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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Supporting Information Available: General experimental procedures, full spectral data for all new compounds, and copies of NMR spectra for all new compounds without elemental analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) In this sequence, *cis*-**17c** was obtained in 14% yield along with *trans*-**17c**. *cis*-**17c** could be converted into *trans*-**17c** by the treatment with NaOMe.