Friedel–Crafts Alkylation of Indoles by *tert*-Enamides in Acetic Acid

Ying Zhang, Jing Jiang, Xue-Qiang Chu, Ran Jiang, Xiao-Ping Xu,* Dan-Hua Li, Shun-Jun Ji*

Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry, Chemical Engineering and Materials Science, Soochow University, Suzhou 215123, P. R. of China
Fax +86(512)65880307; E-mail: xuxp@suda.edu.cn; E-mail: chemjsj@suda.edu.cn

Received 14 November 2011

Abstract: In acetic acid, Friedel–Crafts alkylation of indoles by *tert*-enamides proceeded effectively in the absence of any catalyst to afford the pharmacologically and biologically active 2-oxo-1-pyrrolidine derivatives in moderate to good yields. The mechanistic study based on the NMR and HRMS analysis shows that the reaction was promoted by acid catalysis. The hydrogen-bond interaction between *tert*-enamides and AcOH may also be responsible for the reaction.

Key words: acetic acid, Friedel–Crafts alkylation, *tert*-enamide, indole

Indole and its derivatives occur in nature and possess a variety of important biological activities.[1] Therefore, a lot of attention has been paid to the modification of the indole motif. To date, a number of methods have been developed for C3-functionalization of indole,[2] due to the fact that the 3-position of indole is the preferred site for electrophilic substitution, and meanwhile C3-functionalized indoles are often featured as pharmaceuticals, such as migraine drug almotriptan and melatonin (**Ia** and **Ib**, Figure 1).[3] In this regard, Friedel–Crafts reaction is one of the most commonly used syntheses for the C3-alkylation of indoles.[4] Among various alkylation reagents, such as alcohols, esters, and olefins, the olefins are always considered to be the best choice because they provide atom-economic processes. It is worthwhile to note that electron-rich alkenes such as enamides, which has been proved to be useful reagents and widely utilized in organic synthesis,[5] were seldomly considered to be convenient candidates for alkylation probably due to their weak electrophilicity.[6]

Amide fragment is also widely featured in pharmacologically and biologically active compounds.[7] For example, melatonin (**Ib**, Figure 1) is a naturally existing compound found in animals, plants, and microbes.[3b] While nefiracetam (**Ic**, Figure 1) has been explored for the treatment of cerebrovascular disease.[8] Compounds possessing both essential units (**Id**, Figure 1) have been discovered to demonstrate good activities for the therapy of common diseases such as attention deficit hyperactivity disorder (ADHD), cardiac arrhythmia, asthmatic syndrome, etc.[9] However, existing methods for the synthesis of these pharmaceutical molecules often suffered from limitations such as metal residue, medium detrimental and narrow substrate scope.[10,11] Thus, a more convenient and environmentally benign protocol is highly desirable. We recently found that the synthesis of oral drugs formulated as **Id** could be achieved by the Friedel–Crafts reaction of indoles and *tert*-enamides under catalyst-free conditions, and acetic acid was confirmed to be the appropriate medium for this reaction. Here, we report these results.

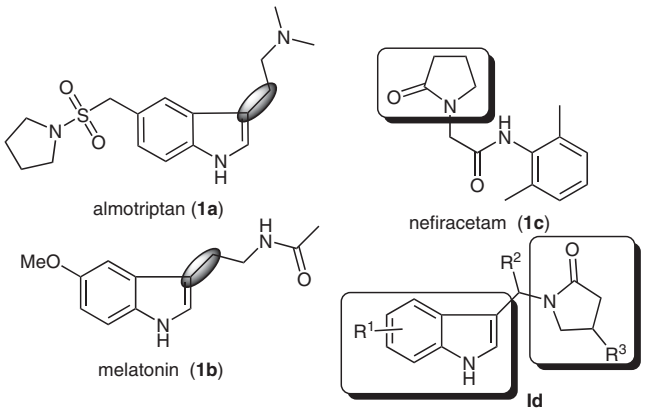
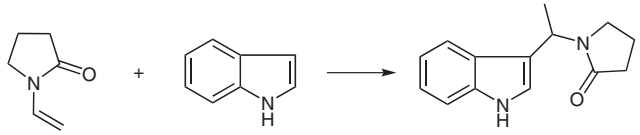


Figure 1

Zhang and co-workers have demonstrated that acetic acid had no catalytic activity for this reaction.[11] However, research work on a multicomponent reaction showed that acetic acid served as a solvent instead of a catalyst in promoting the reaction effectively.[12] Based on these results, we also carefully conducted the similar examination on the present reaction. 1-Vinylpyrrolidin-2-one (**1a**) and indole (**2a**) were employed as the template substrates to test the reaction in 2.0 mL ethanol at room temperature in the presence of 10 mol% acetic acid (Table 1, entry 1). Just as reported, no desired product was detected. Under the same conditions, increasing the acetic acid loading from 50 mol% to 150 mol% also gave disappointing results (Table 1, entries 2–4). However, to our surprise, the desired reaction could run well in the presence of 50 mol% acetic acid under the solvent-free conditions. After optimization of the reaction conditions by varying the amount of acetic acid, finally 1 mL acetic acid was proved to be the best suitable condition for the model reaction (Table 1, entries 5–7). On the basis of the above observations, we suppose that acetic acid may act as both reaction catalyst and solvent. In comparison, a sole use of the aprotic solvent *N*,*N*-dimethylformamide was detected to be inert for the reaction (Table 1, entry 8).

SYNLETT 2012, 23, 751–754
Advanced online publication: 28.02.2012
DOI: 10.1055/s-0031-1290605; Art ID: W66711ST

Table 1 The Synthesis of 1-[1-(1*H*-Indol-3-yl)ethyl]pyrrolidin-2-one (**3a**) – Optimization Studies[a]



Entry	Conditions	Time (h)	Yield (%)[b]
1	AcOH (10 mol%), EtOH (2 mL)	24	0
2	AcOH (50 mol%), EtOH (2 mL)	24	0
3	AcOH (100 mol%), EtOH (2 mL)	24	0
4	AcOH (150 mol%), EtOH (2 mL)	24	0
5	AcOH (50 mol%)	24	72
6	AcOH (1 mL)	7	85
7	AcOH (2 mL)	7	83
8	DMF (2 mL)	24	0

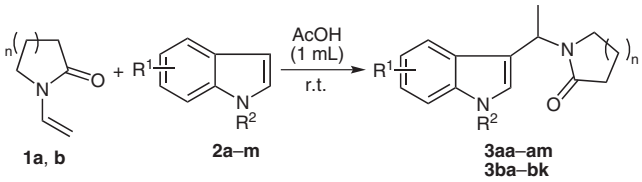
[a] Reactions were performed with **1a** (1.0 mmol), **2a** (1.0 mmol) at r.t.
[b] Isolated yields.

With the optimal conditions established, the scope of indoles to the protocol was explored, and the results are summarized in Table 2. As for the reaction with 1-vinylpyrrolidin-2-one (**1a**), various substituted indoles, bearing either electron-donating or electron-withdrawing substituents, reacted efficiently to give the desired products in good to excellent yields. The position of a substituent at the π-system of indole negligibly affected the reaction except at 3-position (Table 2, entries 2, 5, 6, 10–12). In the indole π-system, C3 was well known to display the strongest nucleophilic ability among all the atoms.[14] So, in our investigation, the reaction using 3-acetyl indole did not take place at all (Table 2, entry 4), while the use of 3-methyl indole led to an alkylation at its 2-position with moderate efficiency (Table 2, entry 13). 1-Vinylazepan-2-one (**1b**), another *tert*-enamide possessing a similar framework to 1-vinylpyrrolidin-2-one, was also introduced. From the results shown in Table 2, we can see that the reactivity of 1-vinylazepan-2-one (**1b**) was apparently lower than that of 1-vinylpyrrolidin-2-one (**1a**), which may be due to the steric hindrance arising from the bigger ring system of **1b**. The behavior also can be seen from the facts that 2-Me, 2-Ph, and 4-Me indoles gave relatively low yields of the corresponding products (Table 2, entries 15–17). In addition, it was found that the electronic effect had a slight influence on the reactions of **1a** and **1b**. For example, 5-Me indole afforded a higher yield of the expected product than 5-nitro indole under identical conditions (Table 2, entries 6, 9, 18 and 21).

With the success of the above protocol using indoles, next we investigated other electron-rich π-systems such as 1,3,5-trimethoxyl benzene (**2n**). It was fortunately found that the reactions could also proceed smoothly in acetic acid (Scheme 1). Monoalkylated products **3an** and **3bn** could be obtained in moderate to good yields with high selectivity.

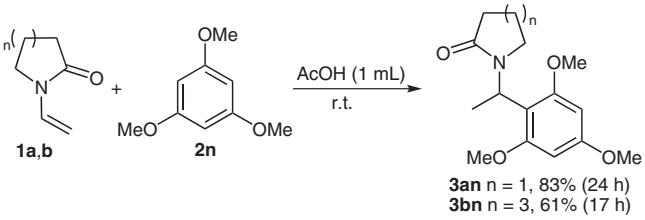
After we successfully accomplished the Friedel–Crafts reaction between electron-rich aromatic rings and *tert*-enamides, we turned our attention to the reaction mechanism. In order to make the relationship between substrate and solvent clear, we compared the ^{1}H NMR and ^{13}C NMR of 1-vinylpyrrolidin-2-one (**1a**) in deuterated

Table 2 Reaction of *tert*-Enamides and Various Indoles[a]



Entry	n	R^1	R^2	Product	Time (h)	Yield (%)[b]
1	**1a** 1	**2a** H	H	**3aa**	7	85
2		**2b** 2-Me	H	**3ab**	7	89
3		**2c** 2-Ph	H	**3ac**	7	84
4		**2d** 3-Ac	H	**3ad**	24	–
5		**2e** 4-Me	H	**3ae**	17	83
6		**2f** 5-Me	H	**3af**	7	89
7		**2g** 5-Br	H	**3ag**	9	78
8		**2h** 5-MeO	H	**3ah**	18	83
9		**2i** 5-NO_2	H	**3ai**	12	81
10		**2j** 6-Me	H	**3aj**	12	72
11		**2k** 7-Me	H	**3ak**	12	83
12		**2l** H	Me	**3al**	24	>99
13		**2m** 3-Me	H	**3am**	24	41[c]
14	**1b** 3	**2a** H	H	**3ba**	17	88
15		**2b** 2-Me	H	**3bb**	18	43
16		**2c** 2-Ph	H	**3bc**	19	66
17		**2e** 4-Me	H	**3be**	19	40
18		**2f** 5-Me	H	**3bf**	24	73
19		**2g** 5-Br	H	**3bg**	18	75
20		**2h** 5-MeO	H	**3bh**	9	86
21		**2i** 5-NO_2	H	**3bi**	24	61
22		**2j** 6-Me	H	**3bj**	24	72
23		**2k** 7-Me	H	**3bk**	17	82

[a] Reactions were performed with *N*-vinyl compounds (1.0 mmol) and indoles (1.0 mmol) in AcOH (1.0 mL) at room temperature.[13]
[b] Isolated yields.
[c] 2-Alkylated product was obtained.



Scheme 1 The reactions between *tert*-enamides and electron-rich benzene systems

chloroform (red) and acetic acid (blue, Figure 2). It was found that peaks for H(c) and C(c) shifted downfield obviously. However, we did not detect the typical signal of sp^3 carbon as previously described.[15] Thus, a deuterium-exchange experiment was carried out as well to examine if there is a possibility that the reaction proceeded via a classic acid-catalysis process. After treatment of **1a** with excessive CD_3COOD, partial deuteration of **1a** was observed from HRMS analysis (see Supporting Information). It may be due to the existence of a fast equilibrium between **1a** and its protonated iminium species (Scheme 2). So we supposed that the reaction mainly proceeded via an acid-catalysis way. Nevertheless, we could not rule out the possible involvement of a hydrogen-bond interaction.

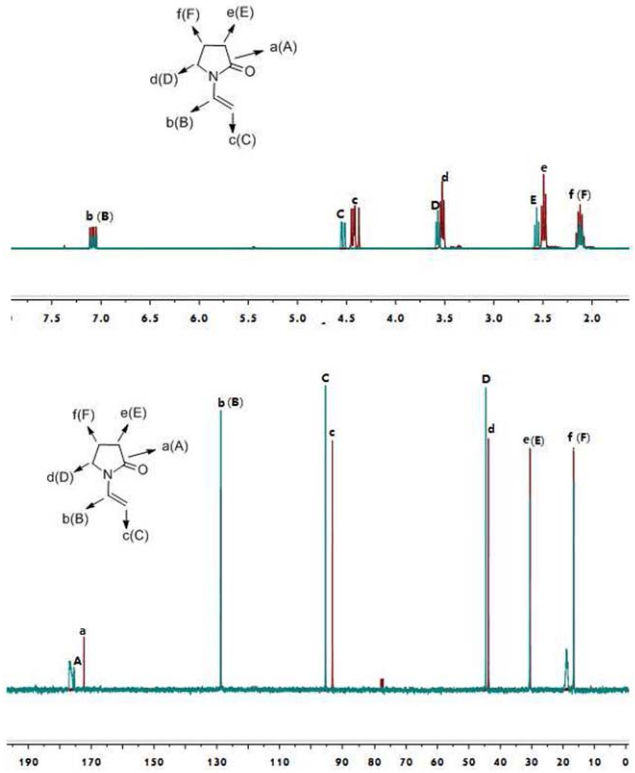


Figure 2 The NMR spectra of 1-vinylpyrrolidin-2-one (**1a**) in deuterated $CHCl_3$ (red) and AcOH (blue)

In summary, we disclosed an efficient way for a useful Friedel–Crafts reaction of electron-rich aromatic rings with *tert*-enamides. The protocol has advantages such as wider substrate scope, mild reaction conditions, and no catalyst participation. By employing this method, a series of analogues of pharmaceuticals were facilely synthesized. A mechanistic study shows the reactions may occur via an acid-catalysis process.

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

Acknowledgment

The work was partially supported by the National Natural Science Foundation of China (No. 21042007, 21172162), Natural Science Basic Research of Jiangsu Province for Higher Education (No. 10KJB150016), a Research Grant from the Innovation Project for Graduate Student of Jiangsu Province (CX10B-033Z), Innovation project for undergraduate student-state level (No. 101028514), and Key Project in Science & Technology Innovation Cultivation Program of Soochow University.

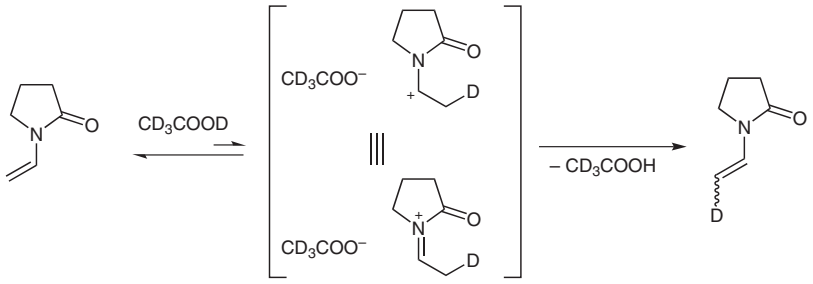
References and Notes

(1) (a) Gribble, G. W. *Comprehensive Heterocyclic Chemistry II*, Vol. 2; Katritzky, A. R.; Ress, C. W.; Scriven, E. F. V.; Bird, C. W., Eds.; Pergamon Press: Oxford, **1996**, 270. (b) *Indoles*; Sundberg, R. J., Ed.; Academic Press: London, **1996**. (c) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893. (d) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875.

(2) (a) Joule, J. A. *Indole and its Derivatives,* In *Science of Synthesis (Houben-Weyl: Methods of Molecular Transformations)*, Vol. 10; Thomas, E. J., Ed.; Thieme: Stuttgart, **2000**, Chap. 10.13. (b) Bandini, M.; Eichholzer, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 9608. (c) Gribble, G. W. *Pure Appl. Chem.* **2003**, *75*, 1417. (d) Zeng, M.; You, S.-L. *Synlett* **2010**, 1289.

(3) (a) Pascual, J.; Cabarrocas, X. *Headache* **2002**, *42*, 28. (b) Paredes, S. D.; Korkmaz, A.; Manchester, L. C.; Tan, D.-X.; Reiter, R. J. *J. Exp. Bot.* **2009**, *60*, 57.

(4) (a) Trost, B. M.; Fleming, I. *Organic Synthesis*, Vol. 3; Pergamon Press: Oxford, **1991**, Chap. 1.8, 293. (b) Meima,



Scheme 2 The possible status of **1a** in CD_3COOD

G. R.; Lee, G. S.; Garces, J. M. In *Friedel–Crafts Alkylation*; Sheldon, R. A.; Bekkum, H., Eds.; Wiley-VCH: New York, **2001**, 151.

(5) (a) Yang, L.; Deng, G.; Wang, D.-X.; Huang, Z. T.; Zhu, J.; Wang, M.-X. *Org. Lett.* **2007**, *9*, 1387. (b) Meth-Cohn, O.; Westwood, K. T. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1173. (c) Shono, T.; Matsumura, Y.; Tsubata, K.; Sugihara, Y.; Yamane, S.-i.; Kanazawa, T.; Aoki, T. *J. Am. Chem. Soc.* **1982**, *104*, 6697. (d) Carbery, D. R. *Org. Biomol. Chem.* **2008**, *6*, 3455. (e) Yang, L.; Wang, D.-X.; Zheng, Q.-Y.; Pan, J.; Huang, Z. T.; Wang, M.-X. *Org. Biomol. Chem.* **2009**, *7*, 2628. (f) Nilson, M. G.; Funk, R. L. *Org. Lett.* **2006**, *8*, 3833. (g) Yang, L.; Tong, S.; Wang, D.-X.; Huang, Z.-T.; Zhu, J.; Wang, M.-X. *Synlett* **2010**, 927. (h) Yang, L.; Zheng, Q.-Y.; Wang, D.-X.; Huang, Z.-T.; Wang, M.-X. *Org. Lett.* **2008**, *10*, 2461. (i) Yang, L.; Wang, D.-X.; Huang, Z.-T.; Wang, M.-X. *J. Am. Chem. Soc.* **2009**, *131*, 10390. (j) Yang, L.; Lei, C.-H.; Wang, D.-X.; Huang, Z.-T.; Wang, M.-X. *Org. Lett.* **2010**, *12*, 3918.

(6) (a) Terada, M.; Sorimachi, K. *J. Am. Chem. Soc.* **2007**, *129*, 292. (b) Jia, Y.-X.; Zhong, J.; Zhu, S.-F.; Zhang, C.-M.; Zhou, Q.-L. *Angew. Chem. Int. Ed.* **2007**, *46*, 5565.

(7) (a) Akiyama, S.; Niki, T.; Utsunomiya, T.; Watanabe, J.; Nishioka, M.; Suzuki, H.; Hayasaka, F.; Yamagishi, K. EP 1020447, **2000**. (b) Gobert, J.; Giurgea, C.; Geerts, J.-P.; Bodson, G. EP 172096, **1985**. (c) Kenda, B.; Michel, P.; Quesnel, Y. WO 2005054188, **2005**. (d) Gobert, J.; Geerts, J.-P.; Bodson, G. EP 0162036, **1985**. (e) Schmiesing, R. J.; Murray, R. J. US 5334720, **1994**.

(8) Robinson, R. G.; Jorge, R. E.; Clarence-Smith, K.; Starkstein, S.; Neutropsychiatry, J. *Clin. Neurosci.* **2009**, *21*, 144.

(9) Kenda, B.; Quesnel, Y.; Ates, A.; Michel, P.; Turet, L.; Mercier, J. WO 2006128693, **2006**.

(10) (a) Andreanti, F.; Andrisano, R.; Case, C. D.; Tramontini, M. *J. Chem. Soc.* **1970**, 1157. (b) Nunomoto, S.; Kawakami, Y.; Yamashita, Y.; Takeuchi, H.; Eguchi, S. *J. Chem. Soc., Perkin Trans. 1* **1990**, 111. (c) Zhang, Z.; Wang, X.; Widenhoefer, R. A. *Chem. Commun.* **2006**, 3717.

(11) Niu, T. M.; Huang, L. H.; Wu, T. X.; Zhang, Y. H. *Org. Biomol. Chem.* **2011**, *9*, 273.

(12) Chen, T.; Xu, X.-P.; Ji, S.-J. *J. Comb. Chem.* **2010**, *12*, 659.

(13) **General Procedure for the Reaction of *N*-Vinyl Compound with Nucleophile (Take the Reaction of 1-Vinylpyrrolidin-2-one with Indole as Example)**
To a mixture of 1-vinylpyrrolidin-2-one (0.1111g, 1.0 mmol) and indole (0.1171g, 1.0 mmol), AcOH (1.0 mL) was added. The reaction system was stirred vigorously at r.t. until the starting materials were completely consumed as indicated by TLC analysis. Then the mixture was poured into H_2O, neutralized by $NaHCO_3$, and extracted by CH_2Cl_2 (2 × 15 mL). The combined organic layer was washed with brine, dried with anhyd Na_2SO_4, and evaporated under the reduced pressure. The residue was purified by flash column chromatography with EtOAc and PE as eluents to afford pure product **3aa** (0.194 g, yield 85%).
1-[1-(2-Methyl-1*H*-indol-3-yl)ethyl]pyrrolidin-2-one (3ab)
White solid; mp 176–177 °C. IR (KBr): 3317, 2974, 2933, 2876, 1656, 1491, 1435, 1287, 1198, 1051, 749 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.72 (d, *J* = 6.9 Hz, 3 H), 1.82–2.00 (m, 2 H), 2.32–2.41 (m, 2 H), 2.48 (s, 3 H), 3.11–3.19 (m, 1 H), 3.53–3.61 (m, 1 H), 5.75 (q, *J* = 7.2 Hz, 1 H), 7.05–7.12 (m, 2 H), 7.27 (t, *J* = 1.8 Hz, 1 H), 7.70 (d, *J* = 7.5 Hz, 1 H), 8.07 (br s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.3, 135.6, 133.9, 128.3, 121.3, 119.9, 119.6, 111.0, 110.8, 44.0, 44.0, 31.9, 18.1, 18.0, 13.0. HRMS (EI): *m/z* calcd for $C_{15}H_{18}N_2O$: 242.1419; found: 242.1420.

(14) Lakhdar, S.; Westermaier, M.; Terrier, F.; Goumont, R.; Boubaker, T.; Ofial, A. R.; Mayr, H. *J. Org. Chem.* **2006**, *71*, 9088.

(15) Jiang, R.; Wu, X.-J.; Zhu, X.; Xu, X.-P.; Ji, S.-J. *Eur. J. Org. Chem.* **2010**, 5946.

