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Fischer Indole Synthesis in Low Melting Mixtures

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ABSTRACT

Functionalized indoles are synthesized under mild conditions in a tartaric acid−dimethylurea melt. The melt serves as the solvent and as the catalyst. Under these reaction conditions, sensitive functional groups such as *N*-Boc, *N*-Cbz, or azides are stable, and indolenines are obtained regioselectively in excellent yields. The practical use of the method is demonstrated in the synthesis of the hormone melatonin.

Organic transformations are typically carried out in solution phase,[1] but as most organic solvents are toxic, flammable and may lead to environmental hazards[2] ongoing efforts aim to replace hazardous solvents by nontoxic and environmentally friendly reaction media.[3] Some of the "green" solvents, which are finding their way into chemical processes are water,[4] polyethylene glycol,[5] $scCO_2$,[6] ionic liquids[7] and fluorous solvents.[8]

We have recently established low melting mixtures comprising of urea, carbohydrates and inorganic salts as alternative renewable reaction media for organic transformations.[9] The melt consists of nontoxic and nonvolatile compounds readily available from natural resources. The melt mixtures are environmentally friendly, as they are easily biodegradable. Since the polarity of these melts is high, reactions involving a polar transition state are usually favored in this medium.[10] We have applied the low melting mixtures for a variety of organic transformations such as cycloaddition reactions, coupling reactions, synthesis of glycosyl ureas, dihydropyrimidinones (DHPMs) and pyrimidopyrimdine-diones.[11]

The indole moiety is one of the most ubiquitous heterocyclic scaffolds present in many natural and unnatural compounds with significant biological activities.[12] Consequently, the synthesis of polyfunctional indole derivatives is an important area of research and a variety of modern transition metal catalyzed approaches to indoles have been developed.[13] Among the available methods, the Fischer

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(1) Hailes, H. C. *Org. Process Res. Dev.* **2007**, *11*, 114.
(2) (a) Watson, J. G.; Chow, J. C.; Fujita, E. M. *Atmos. Environ.* **2001**, *35*, 1567. (b) Welton, T. *Chem. Rev.* **1999**, *99*, 2071. (c) Adam, D. *Nature* **2000**, *407*, 938.
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(11) (a) Ilgen., F.; König, B. *Green Chem.* **2009**, *11*, 848. (b) Imperato, G.; Vasold, R.; König, B. *Adv. Synth. Catal.* **2006**, *348*, 2243. (c) Ruß, C.; Ilgen, F.; Reil, C.; Luff, C.; Begli, A. H.; König, B. *Green Chem.* **2011**, *13*, 156. (d) Gore, S; Baskaran, S; König, B. *Green Chem.* **2011**, *13*, 1009. (e) Gore, S; Baskaran, S.; König, B. *Adv. Synth. Catal.* **2012**10.1002/adsc.201200257.
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indole synthesis remains the most important and versatile approach for the preparation of biologically important indole derivatives (Figure 1).[14,15]

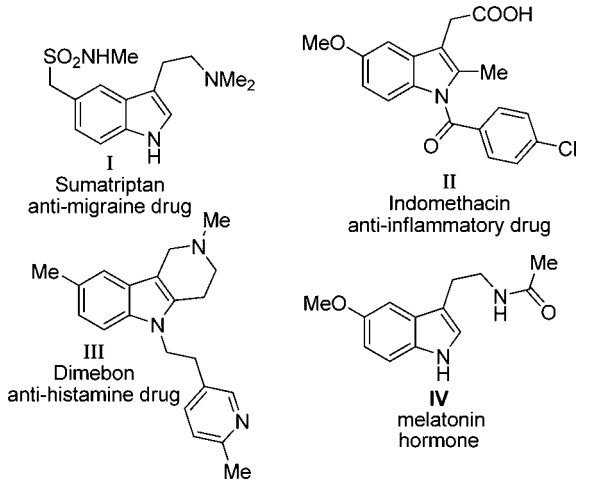
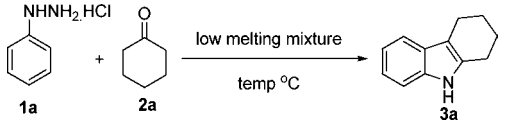


Figure 1. Biologically active indoles.

Ever since the discovery of the Fischer indole synthesis, different catalysts have been explored to effect the cyclization of aryl hydrazones derived from enolizable ketones and aldehydes. Thus, various protocols based on the use of Lewis acids ($ZnCl_2$, $TiCl_4$, PCl_3),[16] Brønsted acids (HCl, H_2SO_4, PPA, AcOH, TsOH),[17] solid acids (zeolite, montmorillonite clay)[18] and solid phase synthesis[19] have been developed for the preparation of indoles. However, many of the reported methods suffer from drawbacks such as harsh or sensitive reaction conditions, use of hazardous reagents or limited substrate scope. Recently, the Fischer indole synthesis has been reported utilizing ionic liquids.[20,21] We report now a very practical and environmentally benign Fischer indole synthesis employing low melting L-(+) tartaric acid (TA)−dimethyl urea (DMU) mixture.

Table 1. Fischer Indole Synthesis from Phenylhydrazine and Cyclohexanone in Different Melts[a]



entry	melt	temp (°C)	time (h)	yield (%)
1	Citric acid:DMU 40:60	65	0.5	80
2	**L-(+)-tartaric acid:DMU 30:70**	**70**	**0.25**	**97**
3	Sorbitol:urea:NH_4Cl 70:20:10	67	1.0	71

[a] Reaction conditions: phenylhydrazine·HCl (1 mmol), cyclohexanone (1 mmol) in 1.5 g of melt.

Since the Fischer indole synthesis typically requires acidic or thermal conditions, we have investigated melt systems consisting of an organic acid as one of the melt components. Citric acid−DMU (40:60) melt (65 °C) was chosen as catalyst and as the reaction medium for the one pot Fischer indole synthesis. A model reaction of phenyl hydrazine and cyclohexanone was carried out in citric acid: DMU melt at 65 °C. To our delight, within 0.5 h, the corresponding tetrahydrocarbazole **3a** was obtained in good yield (entry 1, Table 1). In order to optimize the reaction conditions, the Fischer indole synthesis was carried out in various melt media and some of the results are summarized in Table 1. The L-(+)-TA:DMU (30:70) melt (70 °C) was found to be the best melt medium in terms of reaction rate and yield (entry 2, Table 1).[22]

With these optimized conditions, the scope of the Fischer indole synthesis in melt was investigated using various carbonyl compounds. A variety of cyclic ketones reacted smoothly with phenyl hydrazine to furnish the corresponding indole derivatives in excellent yields (entry 1, Table 2). Phenyl acetaldehyde provides the corresponding indole derivative in good yield (entry 3, Table 2). Interestingly, less reactive aromatic ketones, such as 1-indanone and propiophenone, also provide the corresponding indole derivatives in good yields (entry 6 and 7, Table 2).

Under the reaction conditions, cyclic enol ethers dihydropyran and dihydrofuran reacted smoothly to give the corresponding functionalized indole derivatives in very good yields (entry 9 and 10, Table 2).

In addition, the optically active ketoester **2n** on treatment with phenyl hydrazine afforded, with excellent regioselectivity, the corresponding indole derivative **3n**, an important intermediate in the total synthesis of the indole alkaloid Tubifolidine.[23]

(13) For selected recent examples of indole synthesis, see: (a) Ackermann, L. *Org. Lett.* **2005**, *7*, 439. (b) Asao, N.; Aikawa, H. *J. Org. Chem.* **2006**, *71*, 5249. (c) Würtz, S.; Rakshit, S.; Neumann, J. J.; Droge, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2008**, *47*, 7230. (d) Stuart, D. R.; Bertrand-Laperle, M.; Burgess, K. M. N.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 16474.

(14) For reviews, see: (a) Robinson, B. *Chem. Rev.* **1963**, *63*, 373. (b) Robinson, B. *Chem. Rev.* **1969**, *69*, 227. (c) Gribble, G. W. *J. Chem . Soc., Perkin Trans. 1* **2000**, 1045.

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(22) Since L-(+)-TA is relatively cheaper than DL-TA, the L-(+)-TA is used as one of the melt components in our studies.

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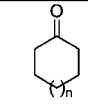
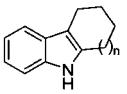
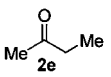
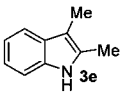
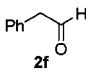
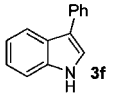
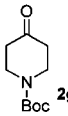
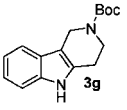
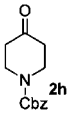
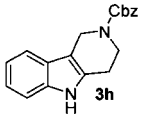
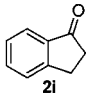
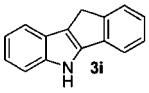
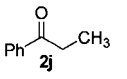
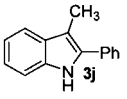
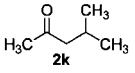
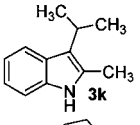
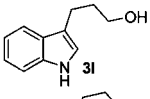
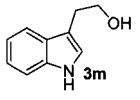
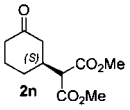
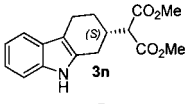
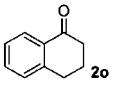
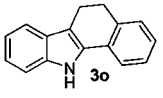
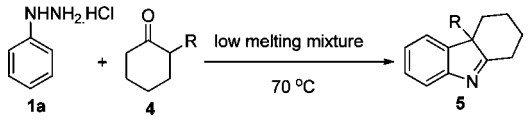
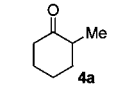
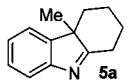
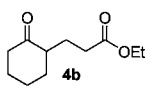
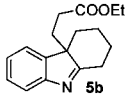
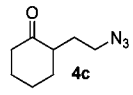
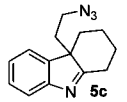
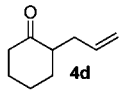
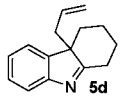
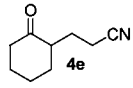
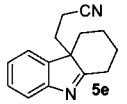
Table 2. Fisher Indole Synthesis from Aldehyde/Ketone and Phenyl Hydrazine in TA:DMU Melt[a]

entry	ketone/ aldehyde	indole	time (h)	yield[b] (%)
1				
	n = 1:**2a**	n = 1:**3a**	0.25	97
	2:**2b**	2:**3b**	1.0	98
	3:**2c**	3:**3c**	1.5	96
	0:**2d**	0:**3d**	0.5	97
2	 **2e**	 **3e**	0.5	88
3	 **2f**	 **3f**	0.25	87
4	 **2g**	 **3g**	3.0	85
5	 **2h**	 **3h**	0.5	94
6	 **2i**	 **3i**	1.5	97[c]
7	 **2j**	 **3j**	5.0	97[c]
8	 **2k**	 **3k**	1.5	95
9	 **2l**	 **3l**	0.5	80
10	 **2m**	 **3m**	1.0	90
11	 **2n**	 **3n**	0.75	97
12	 **2o**	 **3o**	0.75	96[c]

[a] Reaction conditions: ketone/aldehyde (1 mmol), phenyl hydrazine·HCl (1 mmol) in L-(+)-TA:DMU melt at 70 °C. [b] Isolated yield. [c] At 90 °C in L-(+)-TA:DMU melt.

Table 3. Fischer Indole Synthesis Using α-Substituted Ketones[a]



entry	ketone	indole	time (h)	yield[b] (%)
1	 **4a**	 **5a**	0.5	99
2	 **4b**	 **5b**	0.5	94
3	 **4c**	 **5c**	0.5	92
4	 **4d**	 **5d**	0.25	90
5	 **4e**	 **5e**	0.5	90

[a] Reaction conditions: ketone (1 mmol), phenyl hydrazine·HCl (1 mmol) in L-(+)-TA:DMU melt at 70 °C. [b] Isolated yield.

This method is equally efficient for the synthesis of functionalized indolenines, common structural units present in many biologically active alkaloids.[24] Thus, a variety of unsymmetrical α-substituted ketones on treatment with phenyl hydrazine gave the corresponding indolenine[25] derivatives as a single regioisomer (entry 1– 5, Table 3). Under mild conditions, several synthetically useful indolenines bearing allyl and alkyl (ester, azido and cyano) side chains were obtained in excellent yields (entry 1–5, Table 3).

Moreover, the reaction works equally well with a variety of aryl hydrazines having electron donating as well as electron withdrawing substituents, and the results are summarized in Table 4. Since the reaction conditions are mild, several functional groups such as -*N*-Boc, -N_3, -COOEt, -*N*-Cbz, allyl and -CN are found to be stable under the reaction conditions. To the best of our knowledge, for the first time the *N*-Boc functional group is found to be stable under Fischer-indole synthesis conditions.[26]

Moreover, the melt medium can be readily recovered and recycled.[27] The efficiency and stability of the melt mixture was found to be very good even after three cycles; the results are summarized in Table 5.

We next employed the method for the synthesis of the hormone melatonin as shown in Scheme 1. Compound **9** upon treatment with **2m** under melt conditions gave indole

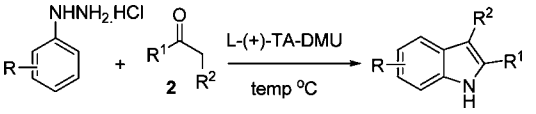
(24) For indolenines as a building block in total synthesis, see: (a) Li, C.; Chan, C.; Heimann, A. C.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 1444. (b) Sapi, J.; Dridi, S.; Laronze, J.; Sigaut, F.; Patigny, D.; Laronze, J. -Y.; Lévy, J. *Tetrahedron* **1996**, *52*, 8209. (c) Vercauteren, J.; Massiot, G.; Levy, J. *J. Org. Chem.* **1984**, *49*, 3230.

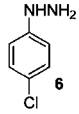
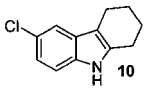
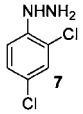
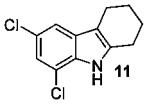
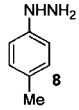
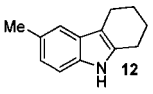
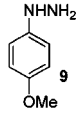
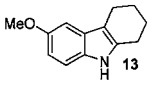
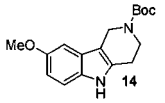
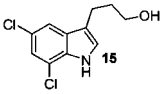
(25) No asymmetric induction was observed under L-(+)-TA:DMU melt condition.

(26) (a) Park, I.-K.; Suh, S.-E.; Lim, B.-Y.; Cho, C.-G. *Org. Lett.* **2009**, *11*, 5454. (b) Bonjoch, J.; Diaba, F.; Pagès, L.; Pérez, D.; Soca, L.; Miralpeix, M.; Vilella, D.; Anton, P.; Puig, C. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4299.

(27) After removal of water under a vacuum, the melt mixture is recovered and recycled in the next cycle without any purification.

Table 4. Fischer Indole Synthesis from Aldehyde/Ketone and Different Aryl Hydrazines in L-(+)-TA:DMU Melt[a]



entry	aryl hydrazine. HCl	ketone/ aldeh- yde	indole	time (h)	yield[b] (%)
1		**2a**		0.5	97
2		**2a**		2.0	90[c]
3		**2a**		0.25	96
4		**2a**		0.25	95
5	**9**	**2g**		2.0	88
6	7	**2l**		0.5	85

[a] Reaction conditions: aldehyde/ketone (1 mmol), aryl hydrazine (1 mmol) in L-(+)-TA:DMU melt at 70 °C. [b] Isolated yield. [c] At 90 °C in L-(+)-TA -DMU melt.

Table 5. Recyclability of TA:DMU Melt in the Reaction of 4-Chlorophenyl Hydrazine and Cyclohexanone[a]

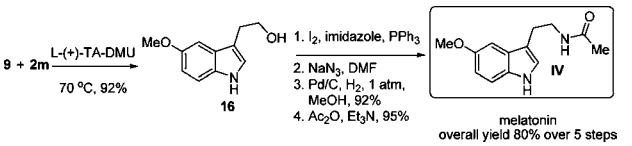
entry	cycle	time (min)	yield[b] (%)
1	1	30	97
2	2	40	94
3	3	45	92

[a] Reaction conditions: cyclohexanone (1 mmol), 4-chlorophenyl hydrazine·HCl (1 mmol) in L-(+)-TA:DMU melt at 70 °C. [b] Isolated yield.

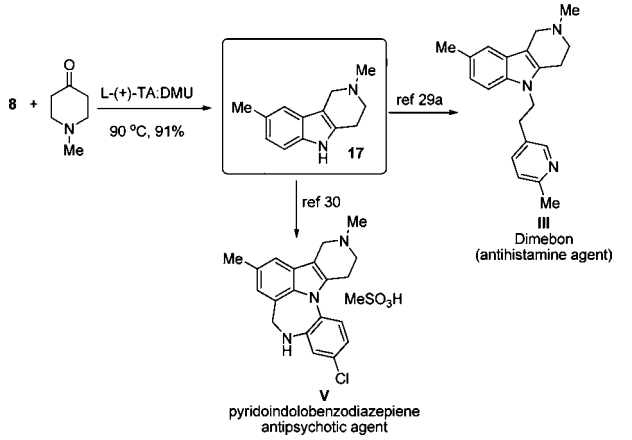
derivative **16**, which was further converted to melatonin in a few steps.

The applicability of the protocol was further demonstrated in the synthesis of indole derivative **17**, a key intermediate in the synthesis of the antihistamine agent Dimebon[28] and the antipsychotic agent pyridoindolobenzodiazepiene.[29] *N*-Methyl piperidone upon treatment with 4-methyl phenyl hydrazine reacted smoothly to yield tetrahydrocarboline **17** in 91% yield (Scheme 2).

Scheme 1. Synthesis of Hormone Melatonin



Scheme 2. Formal Synthesis of Dimebon (Latrepirdine) and Pyridoindolobenzodiazepiene



The work up of this reaction is very simple. Solid indoles can be readily obtained by simple filtration followed by recrystallization. In most of cases, the crude indole was obtained in more than 95% purity.

In summary, we have developed an efficient and environmentally benign Fischer indole synthesis in L-(+) TA: DMU melt under mild and additive free conditions. The melt plays a dual role as solvent and as catalyst. Because of the mild reaction conditions, various sensitive functional groups, such as -N_3, -*N*-Cbz and -*N*-Boc are stable under these conditions. The melt medium can be readily recovered and recycled, if desired. The examples illustrate the wide applicability for the synthesis of bioactive indoles.

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Supporting Information Available. Detailed experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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(29) Zhang, L. -H.; Meier, W.; Wats, E.; Costello, T. D.; Ma, P.; Ensinger, P. O.; Rodgers, J. M.; Jacobson, I. C.; Rajagopalan, P. *Tetrahedron Lett.* **1995**, *36*, 8387.