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Mild, efficient Fischer indole synthesis using 2,4,6-trichloro-1,3,5-triazine (TCT)

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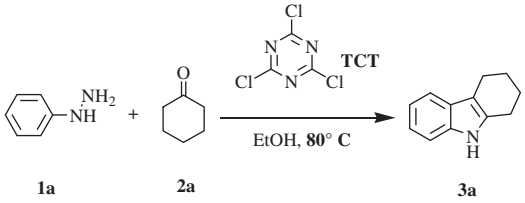
ABSTRACT

Mild and efficient protocol for the Fischer indole synthesis using TCT has been described. TCT serves as a mild and inexpensive catalyst. Under these conditions several functional groups such as ester, cyano, sulfone, amides, and ethers are tolerated. By this method, many functionalized analytically pure indoles were prepared easily without the need of purification.

2,4,6-Trichloro-1,3,5-triazine (TCT) is an inexpensive, readily available chemical in the laboratory. This compound was used as a starting material for the synthesis of various heterocycles.[1,2] Recently TCT has served as an inexpensive, nonvolatile, and easy to handle reagent for various organic transformations.[3–6] For instance, TCT promotes Beckman rearrangement,[7] sulfide to sulfone oxidation,[8] Swern oxidation,[9] Lossen rearrangement,[10] sulfonyl chloride preparation,[11] and Friedel–Craft acylation.[12] TCT is often used for functional group transformations such as carboxylic acid into esters, amides, and peptides,[13] and sulfonic acids into sulfonamides.[14] Furthermore, it has been used in the construction of heterocyclic ring like 1,3,4 oxadiazoles,[15] 2-aryl benzothiazoles,[16] and bisindoles[17] and in the multicomponent reaction.[18–20] TCT is also employed in the solid support reactions.[21,22] Interestingly, in all the above examples the product isolation was easy and yields were ranging from good to excellent. Hence prompted by these results, we applied TCT for the Fisher indole synthesis.

Indole is a versatile heterocyclic structure available in variety of compounds with vast biological activities.[23–25] Due to this, indole and its preparation continue to capture the attention of organic and medicinal chemists. Although, many methods are available for the synthesis of indole ring,[26] the Fisher indole synthesis using ketones and arylhydrazines remains the most widely employed synthetic procedure.[27,28] Over here, the acid catalyzed 3,3 sigmatropic rearrangement of aryl hydrazones followed by elimination of ammonia results in an indole skeleton in the presence of various catalysts. Unfortunately, most of the methods suffer due to the use of excessive reagent, strong acidic media, and often long reaction time. Hence mild and expedient protocol is of a significant importance. In continuation of our interest in new organic transformations in indole[29–31] and quinoline[32] synthesis, herein we wish to report the mild and efficient catalyst, TCT for the first time in the synthesis of indoles via Fischer indolization.

As a preliminary study we carried out a reaction between a mole equivalent of phenyl hydrazine hydrochloride (1 equiv), cyclohexanone (1 equiv) in the presence of TCT (0.5 equiv) in dry EtOH as solvent and the reaction mixture was heated to 80 °C (Scheme 1). To our surprise, the reaction gave complete conversion to tetrahydrocarbazole, after 2 h. Encouraged by these results we planned to optimize the reaction conditions. Consequently, a mixture of phenyl hydrazine hydrochloride (**1a**) and cyclohexanone (**2a**) were heated in different solvents and at reduced equivalence of TCT. The results are summarized in Table 1. As shown in the



Scheme 1. Reaction of phenyl hydrazine with cyclohexanone in the presence of TCT.

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Table 1
Optimization of reaction condition

Solvent	TCT in equiv	Temperature in °C	Time in h	Conversion[a] (%)
EtOH	0.5	80	2	100
EtOH	0.1	80	2	100
EtOH	0.05	80	4	80
MeOH	0.1	Reflux	4	90
Moist ACN	0.1	Reflux	4	95
Anhyd.ACN	0.1	Reflux	>6	10[b]
Anhyd THF	0.1	Reflux	>6	20[b]
EtOH	0	80	>6	0[b]
EDC	0.1	Reflux	>6	0[b]

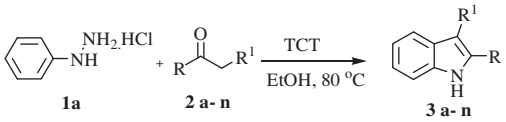
[a] Based on LC–MS.
[b] Hydrazones were observed as major product.

table the best result was obtained when we used 0.1 equiv of TCT at 80 °C temperature in EtOH solvent. Further the decrease in the quantity of TCT slows down the reaction rate. Thus unlike aq HCl which gives unwanted side products (i.e., hydrolysis of hydrazones) TCT is found to be mild and optimum to catalyze the Fischer indolization.

Alternately, we also performed the same reaction without adding TCT. As expected, heating the phenyl hydrazine and ketone in EtOH did not give even traces of indolization but subsequent addition of TCT to the same reaction mixture and further heating for another 2 h afforded the indole product. This confirms the role of TCT in promoting the Fisher indolization (Scheme 1).

With this optimized condition and further to evaluate the scope of this protocol, we attempted Fisher indolization with permutations

Table 2
Reaction of phenyl hydrazine with different ketones and aldehydes (**3a–3n**)



1a **2 a- n** **3 a- n**

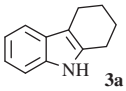
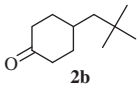
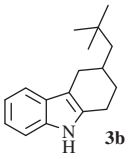
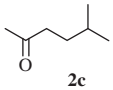
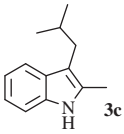
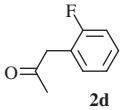
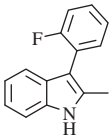
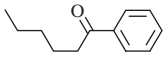
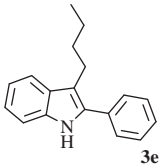
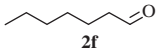
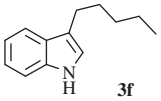
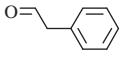
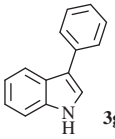
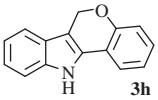
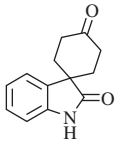
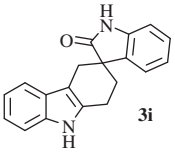
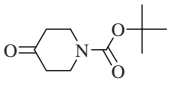
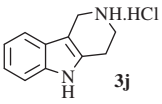
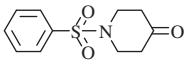
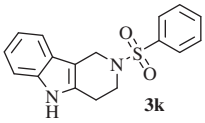
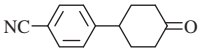
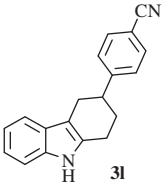
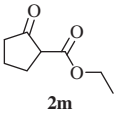
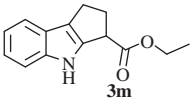
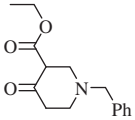
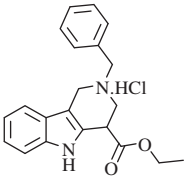
Entry	Ketones/Aldehydes	Product	Yield (%)	Time in h	M.P/Litr (°C)
1	 **2a**	 **3a**	99[a]	2	118–117/116–118[33]
2	 **2b**	 **3b**	98	2	Gummy
3	 **2c**	 **3c**	98	2	Gummy[34]
4	 **2d**	 **3d**	100[a]	2	Gummy
5	 **2e**	 **3e**	95	3	59–61/60–62[35]
6	 **2f**	 **3f**	94	2	45–46 (41–42)[36]
7	 **2g**	 **3g**	95	2	84–86/85–86[37]

Table 2 (*continued*)

Entry	Ketones/Aldehydes	Product	Yield (%)	Time in h	M.P/Litr (°C)
8	 **2h**	 **3h**	50	5	138–139/142[38]
9	 **2i**	 **3i**	98	2.5	142–144
10	 **2j**	 **3j**	95	2	Gummy[b]
11	 **2k**	 **3k**	98[a]	2	185[39]
12	 **2l**	 **3l**	100[a]	2	170
13	 **2m**	 **3m**	95[a]	2.5	Gummy[40]
14	 **2n**	 **3n**	90	3	Gummy[b]

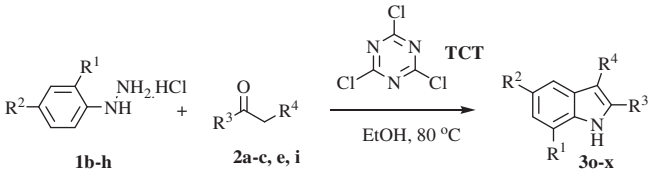
[a] Isolated without purification.
[b] Hygroscopic.

of various phenyl hydrazines and ketones. The results are summarized in Tables 2 and 3.

The reaction with symmetric ketones such as cyclohexanone (**2a**) and neopentylcyclohexanone (**2b**) gave complete conversion, yielding more than 90% of the corresponding indoles (entries 1 and 2). Interestingly, reaction with unsymmetrical ketones such as 5-methyl 2-hexanone (**2c**) affords single regio isomers through the cyclization of the most substituted ene hydrazine (entry 3), which emphasizes the role of TCT as a mild acid catalyst for Fischer indolization. Due to this, the reaction remains incomplete (stopped at hydrazone) in the case of acetophenone. However, the interesting reaction with 4-Boc piperidone (**2j**) gave cyclized γ -carboline with simultaneous deprotection of boc group (entry 10). This in situ deprotection of boc gives directly γ-carboline which is further useful for the derivatization of the amine functionality. The reaction with aldehydes such as heptanal (**2f**) and phenyl acetaldehyde (**2g**) gave an excellent yield of corresponding indoles (entries 6 and 7). Even the less reactive aromatic ketone hexanophenone (**2e**) gave an excellent yield (entry 5). Interestingly, 1-(2-fluorophenyl) acetone (**2d**) reacted faster giving an almost quantitative yield of corresponding indole without any purification (entry 4), while reaction with 4-chromanone (**2h**) took longer reaction time with a moderate yield (entry 8) and a relatively low yield of **8** attributes to the destruction of ether linkage by the nascent HCl. It was notable that several functional groups especially esters (**2m** and **2n**), amides (**2i**), sulfone (**2k**), ether (**2h**) in the ketone substrates (entries 9, 11, 13, and 14), and halogens (**1e**, **1f**, and **1h**) in phenyl hydrazines were tolerated during the course of the reaction (entries 18, 19, and 21). Particularly in the case of 4-(4′-cyanophenyl)cyclohexanone (**2l**), a good yield of carbazole was observed without any solvolysis on the nitrile group (entry 12), but in the case of ethyl-1-benzyl-4-oxopiperidine-3-carboxylate (**2n**) hydrolysis of the product to corresponding acid was observed when we kept the reaction for a longer time. However, in the case of ethyl 2-oxocyclopentanecarboxylate (**2m)** no such hydrolysis was observed.

In continuation, we further studied the scope of this reaction with substituted phenyl hydrazines and the results are summarized in Table 3. The phenyl hydrazines possessing electron donating groups such as methyl (**1b**, **1d**) and isopropyl (**1c**) (entries 15–17), electron withdrawing groups such as chloro (**1e**), fluoro (**1h**), and methoxy (**1g**) are well tolerated to furnish good to

Table 3
Reaction of various phenyl hydrazines with different ketones (**3o–3x**)



1b-h **2a-c, e, i** **3o-x**

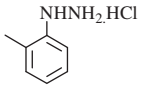
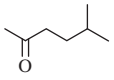
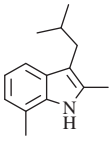
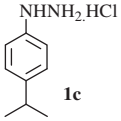
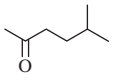
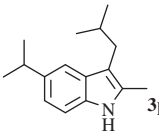
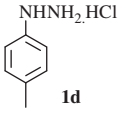
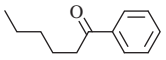
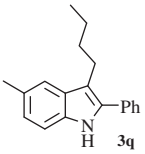
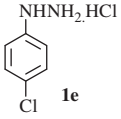
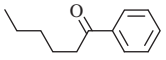
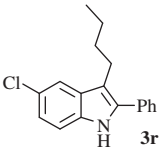
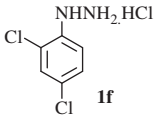
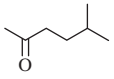
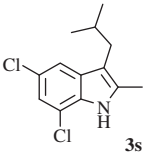
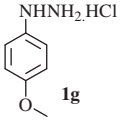
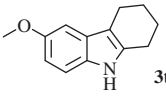
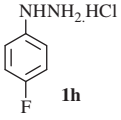
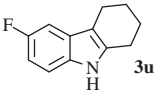
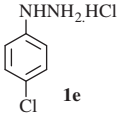
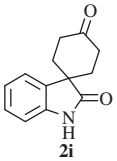
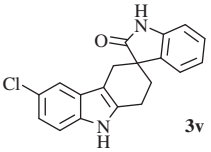
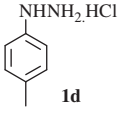
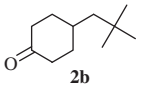
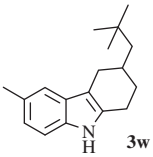
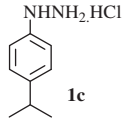
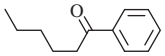
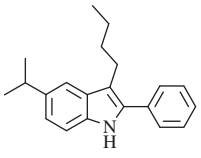
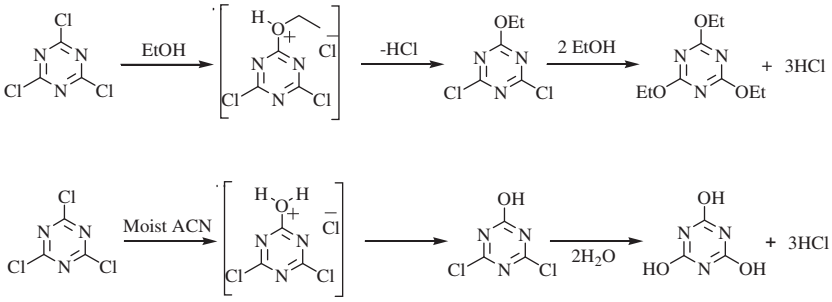
Entry	Phenyl hydrazines	Ketones	Product	Yield (%)	Time in h	Mp/Litr (°C)
15	 **1b**	 **2c**	 **3o**	80	2	Gummy[b]
16	 **1c**	 **2c**	 **3p**	96	2	55–58
17	 **1d**	 **2e**	 **3q**	90[a]	3.5	64–67
18	 **1e**	 **2e**	 **3r**	90	3	82–85
19	 **1f**	 **2c**	 **3s**	98[a]	2	Gummy
20	 **1g**	 **2a**	 **3t**	97	2	87–89/88–90[33]
21	 **1h**	 **2a**	 **3u**	98	2	94–95/93–95[33]
22	 **1e**	 **2i**	 **3v**	99	3	200
23	 **1d**	 **2b**	 **3w**	98	2	Gummy

Table 3 (*continued*)

Entry	Phenyl hydrazines	Ketones	Product	Yield (%)	Time in h	Mp/Litr (°C)
24	 **1c**	 **2e**	 **3x**	90	3	60

[a] Isolated without purification.
[b] Unstable.



Scheme 2. Plausible mechanism in which TCT generates nascent HCl to induce Fischer indolization.

excellent yields of substituted indoles (entries 18, 20, and 21). In addition 2,4 disubstituted phenyl hydrazine (**1f**) also gave an excellent yield of the corresponding indole (entry 19). Even the steric factor due to ortho substitutions (**1b** and **1f)** did not reduce the reaction rate (entries 15 and 19).

It has been noticed that TCT promotes the Fischer indolization via slow liberation of nascent HCl. This happens when nucleophilic EtOH displaces the chloride ion from 1 mol of TCT to give 3 mol of nascent HCl (Scheme 2). Thus liberated HCl catalyzes the hydrazone formation and subsequent cyclization to yield the desired indole product, whereas in the case of anhydrous THF, EDC, and ACN, HCl liberation was not found to catalyze the indolization (Table 1). However, we noticed that the moment we used moist ACN we found indolization. This can be attributed to the moisture in ACN which reacts with TCT to liberate HCl and catalyzes the indolization (Scheme 2).

In summary, we have developed a mild, efficient, and high yielding protocol for the Fischer indolization using TCT as a catalyst. Because of the mild nature of TCT, several functional groups such as ester, amides, sulfone, ethers, and cyano are tolerated. Another significant feature is the ease of product isolation. Pure products are obtained by just evaporation of the solvent, after work-up. Thus a wide variety of biologically active functionalized pure indoles can be prepared by adopting these conditions.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.07.157.

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