Research Article

Cyanuric Chloride-Catalyzed Michael Addition of Indoles to Nitroolefins under Solvent-Free Conditions

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Cyanuric chloride is an inexpensive, efficient, and mild catalyst for the Michael addition of indoles to nitroolefins at 70°C under solvent-free conditions. The simple experimental procedure, solvent-free reaction conditions, utilization of an inexpensive and readily available catalyst, short period of conversion, and excellent yields are the advantages of the present method.

1. Introduction

The indole nucleus is an important structural motif in medicinal chemistry [1–3]. Substituted indoles have been referred to as privileged structures as they are capable of binding to many receptors with high affinity [4–6]. Therefore, the synthesis and selective functionalization of indoles have been the focus of active research over the years [7, 8]. Since the 3-position of the indole is the ideal site for electrophilic attack, 3-substituted indoles are versatile intermediates for the synthesis of a wide variety of indole derivatives. Commonly indole 3-derivatives are prepared by the Michael addition of indoles with β -nitrostyrenes in the presence of dodecyl sulfate scandium(III)salt [9], InCl_3 [10], InBr_3 [11], $\text{Bi}(\text{OTf})_3$ [12], $[\text{Al}(\text{DS})_3] \cdot 3\text{H}_2\text{O}$ [13], SmI_2 [14], I_2 [15], KHSO_4 [16], sulfamic acid [17], $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ [18], β -cyclodextrin [19], $\text{Zn}(\text{OAc})_2$ [20], TiO_2 [21], Montmorillonite K10 [22], CoCl_2 [23]. In view of the importance of the indole 3-derivatives, there still remains the necessity to develop a new methodology.

Cyanuric chloride (2,4,6-Trichlorotriazine, TCT) is a stable, nonvolatile, inexpensive, and safe reagent which has been used synthetically for the preparation of various types of compounds such as 2-aryl-2,3-dihydroquinolin-4(1H)-ones [24], bis(indolyl)methanes [25], N-sulfonyl imines [26], and 14-aryl or alkyl-14-H-dibenzo[*a, j*]xanthenes [27]. In this paper, we wish to report a rapid and highly efficient

method for the Michael addition of indoles to nitroolefins in the presence of TCT at 70°C under solvent-free conditions (Scheme 1).

2. Experimental

General Procedure for the Preparation of 3. A mixture of indoles (1 mmol), nitroolefins (1 mmol), and TCT (0.1 mmol) was heated at 70°C for the appropriate time (Table 2) under wet air atmosphere. The reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature and washed with water. The solid products were purified by column chromatography using acetone-petroleum ether ($v : v = 1 : 8$) as eluent. All the compounds are known and their physical properties are the same as the reported values. ^1H NMR and ^{13}C NMR, and elemental analysis data of all the products match the reported data.

3. Results and Discussion

Initially, we chose indole (**1a**) and the commercially available β -nitrostyrene (**2a**) as starting materials to establish the best conditions for the reaction. The optimum catalyst loading for TCT was found to be 10 mol%. When the amount of the catalyst was decreased to 51 mol%, the yield of the product

SCHEME 1

TABLE 1: Synthesis of 3-(2-nitro-1-phenylethyl)-1H-indole under various conditions^a.

The reaction scheme shows indole (1a) reacting with β-nitrostyrene (2a) in the presence of TCT catalyst, neat, at 70 °C, to produce 3-(2-nitro-1-phenylethyl)-1H-indole (3a).

Entry	TCT (mol%)	T. (°C)	Time (min)	Yield (%) ^b
1	0	70	120	63
2	5	70	45	88
3	10	70	30	97
4	15	70	30	96
5	10	25	120	63
6	10	40	60	71
7	10	50	45	85
8	10	60	30	90
9	10	80	30	96
10	10	90	30	96

^a Reaction conditions: indole (1 mmol); β-nitrostyrene (1 mmol); neat.^b Isolated yield.

3a was reduced considerably but with 15 mol% loading of the catalyst, no further improvement of the yield was observed (Table 1). To screen for the practical temperatures for the solvent-free synthesis, the previous reaction was run in on a 1 mmol scale of substrate at different temperature (Table 1). As shown in Table 1, the reaction at 70 °C proceeded in highest yield among the seven reaction temperatures tested. So 70 °C was chosen for this reaction.

Based on the optimized reaction conditions, a series of 3-(2-nitro-1-arylethyl)-1H-indole derivatives was synthesized. As shown in Table 2, the reaction under solvent-free and 10 mol% TCT conditions gave the corresponding product in good yields. The electronic effects and nature of substituents on the nitroolefins did not show a strongly obvious difference in terms of yields. This protocol can be applied not only to nitroolefins either with electron-withdrawing groups (such as a nitro group, halogen) or electron-donating groups (such as a methoxy group) but also to hetero-aromatic nitroolefins with excellent yields under the same conditions. Substituents

on the indole ring do not have an effect on the adduct formation.

HCl generated in situ, from cyanuric chloride, efficiently catalyzes these reactions. Accordingly, cyanuric chloride (10 mol %) reacts with “incipient” moisture and releases three moles of HCl and cyanuric acid (removable by washing with water) as a by-product. The in situ-generated HCl acts as protic acid and activates the Michael addition. The reaction could be facilitated by wet glass wares or by the presence of wet air. However, the reaction under dry reaction conditions in the presence of MS 4 Å met with failure. Thus, it amply indicates that the “incipient” moisture plays an important role for HCl generation in situ from TCT.

4. Conclusion

In summary, a new catalytic protocol for the Michael addition of indoles to nitroolefins has been developed. Compared with previous reported methodologies, the present protocol features simple work-up, easy, and quick isolation of the

TABLE 2: Michael addition of indoles to nitroolefins catalyzed by TCT under solvent-free condition.

Entry	Indoles	Nitroolefins	Products	Time (min)	Yield (%) ^b	m.p. (°C) (lit.)
1			3a	30	97	101-102 (99-100) [23]
2			3b	30	93	liquid (liquid) [28]
3			3c	30	94	144-146 (146-147) [23]
4			3d	60	89	142-143 (144-146) [28]
5			3e	30	95	100-102 (99-101) [28]
6			3f	20	96	75-76 (77-78) [23]
7			3g	120	87	130-132 (131-133) [23]
8			3h	45	92	143-144 (142) [20]
9			3i	30	93	Semisolid (semisolid) [20]

TABLE 2: Continued.

Entry	Indoles	Nitroolefins	Products	Time (min)	Yield (%) ^b	m.p. (°C) (lit.)
10			3j	20	98	144-145 (145-147) [28]
11			3k	30	92	70-71 (67-68) [17]
12			3l	30	90	85-86 (86-87) [23]
13			3m	60	95	98-99 (95-97) [17]
14			3n	60	89	100-101 (102-103) [23]
15			3o	45	94	129-131 (130-131) [23]
16			3p	60	88	113-115 (112-114) [17]
17			3q	45	90	106-107 (107-108) [17]
18			3r	90	89	141-143 (143-145) [28]

^a Reaction conditions: indoles (1 mmol); nitroolefins (1 mmol); TCT (0.1 mmol); neat; 70 °C.^b Isolated yield.

products, cheap and a catalytic amount of catalyst. This protocol avoids the use of hazardous solvent and toxic metallic catalysts and is of low cost.

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