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$AlCl_3$ as a powerful catalyst for the one-pot preparation of 1,1,3-triheteroaryl compounds

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ABSTRACT

A general and efficient procedure for the synthesis of 1,1,3-triheteroaryl compounds in good to excellent yield at room temperature is developed. The reaction proceeds via mixed Michael and Friedel–Crafts reactions of α,β-enals or α,β-enones and indoles, 2-methylfuran or 2-methylthiophene in the presence of a catalytic amount of $AlCl_3$.

The Michael reaction is generally regarded as one of the most efficient carbon–carbon bond forming reactions, and studies concerning this reaction have played an important role in the development of modern synthetic organic chemistry.[1] The Friedel–Crafts reaction is also another method for the formation of new C–C bonds and has been widely utilized from bench-top experiments to industrial processes.[2] The domino Michael addition of aryl compounds to enals or enones followed by the Friedel–Crafts reaction leads to a series of naturally occurring 1,1,3-triaryl systems which are an important class of bioactive metabolites. For example, tris-indole **3a** was isolated as a racemate from the bacterium *Vibrio parahaemolyticus*.[3] Also, Lee et al. found that 1,1,3-tri(3-indolyl)cyclohexane inhibits the growth of lung cancer cells of xenograft models.[4]

However, these one-pot methods usually make use of expensive catalysts such as $AuCl_3$,[5] and $Zr(OTf)_4$,[6] the hazardous catalyst $SbCl_3$,[7] cerium ammonium nitrate (CAN) and I_2.[8]

Various active heterocycles, especially indoles are important building blocks for biologically active compounds.[9] In our efforts to develop a new method for the synthesis of indolyl compounds,[10] we were interested in the catalytic preparation of 1,1,3-triindolyls from enals or enones and indoles.

Herein, we report on such a process, as well as the appropriate selection of reaction parameters such as type of catalyst and solvent. In initial experiments, indole **1a** and crotonaldehyde (**2a**) were used as model substrates to evaluate suitable reaction conditions for the preparation of tris-indole **3a** (Table 1). A wide range of Brönsted and Lewis acids were examined in acetonitrile as solvent. Protic acids such as silica sulfuric acid (SSA)[11] (Table 1, entry 12), and the metal hydrogen sulfates[12] such as $Al(HSO_4)_3$, $NaHSO_4{\cdot}H_2O$ and $Zr(HSO_4)_4$ (Table 1, entries 13–15) promoted the reaction in 70–97% yields after 4.5 to 24 h. It was also found that Lewis acids such as $Bi(NO_3)_3$, $Ni(NO_3)_3$, $Cd(NO_3)_3$, LiOTf, $ZnCl_2$, and $CoCl_2{\cdot}6H_2O$ were not active in this condensation since no product was observed even after stirring for 24 h (Table 1, entries 9–11 and 19–21). Under the same conditions, $AuCl_3$[5] and $SbCl_3$[7] gave **3a** in 70% yield after 12 h, and 94% yield after 3.5 h, respectively, whilst I_2 and CAN gave 95% and 90% yields of product after 24 h and 3.5 h, respectively (Table 1, entries 4 and 5). Although this reaction proceeded smoothly in the presence of several of the tested catalysts, it was felt that an improved method should still be sought. Surprisingly, the reaction to form 1,1,3-tri(1*H*-indol-3-yl)butane (**3a**) in 96% yield was completed in 8 min when only 10 mol % $AlCl_3$ was used as the catalyst (Table 1, entry 1).

A wide range of solvents were tested to investigate the effect of solvent on the reaction of indole and crotonaldehyde catalysed by $AlCl_3$ (Table 2). The reaction was completed in AcOH in 20 min affording a 97% yield of **3a** (Table 2, entry 2). In the absence of $AlCl_3$, **3a** was obtained in only 70% yield using AcOH as a solvent even after 12 h (Table 2, entry 3). When acetone was used as the solvent, 2,2-bis(indolyl-3-yl)propane was produced in 25% yield as a by-product (Table 2, entry 4). In most of the other solvents

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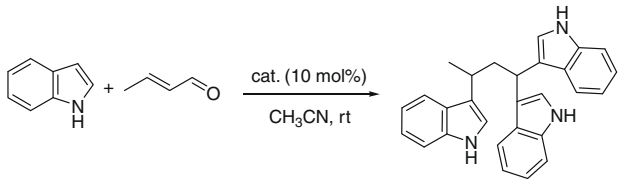
Table 1
Effect of catalyst on the preparation of **3a** from indole (**1a**) and crotonaldehyde (**2a**)



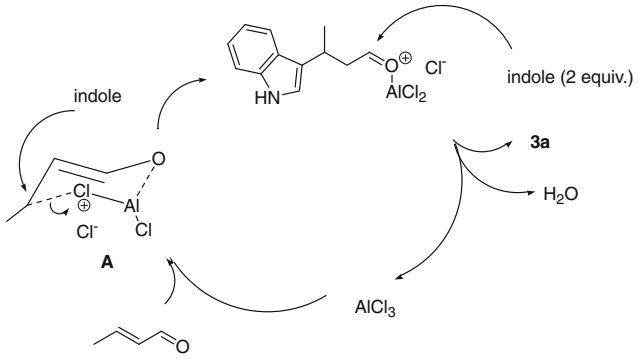
1a **2a** **3a**

Entry	Catalyst	Time (h)	Isolated yield (%)
1	$AlCl_3$	8 min	96
2	$AuCl_3$,[5]	12	70
3	$SbCl_3$,[7]	3.5	94
4	I_2	24	95
5	CAN	3.5	90
6	$FeCl_3{\cdot}6H_2O$	24	94
7	$Fe(NO_3)_3{\cdot}9H_2O$	4	98
8	$Cr(NO_3)_3$	4	98
9	$Bi(NO_3)_3$	24	0
10	$Ni(NO_3)_3$	24	0
11	$Cd(NO_3)_3$	24	0
12	SSA	12.5	97
13	$Al(HSO_4)_3$	4.5	89
14	$NaHSO_4{\cdot}H_2O$	24	88
15	$Zr(HSO_4)_4$	7	70
16	$ZrCOCl_2{\cdot}8H_2O$	1.5	97
17	$ZrCl_4$	4.5	94
18	$Zr(NO_3)_4$	6.5	89
19	LiOTf	24	0
20	$ZnCl_2$	24	0
21	$CoCl_2{\cdot}6H_2O$	24	0

Table 2
Effect of solvent on the preparation of **3a** from indole and crotonaldehyde in the presence of $AlCl_3$

Entry	Solvent	Time (h)	Isolated yield (%)
1	CH_3CN	8 min	96
2	AcOH	20 min	97
3	AcOH[a]	12	50
4	Acetone[b]	12	71
5	CH_2Cl_2	20	92
6	$CHCl_3$	12	93
7	CCl_4	12	91
8	*n*-Hexane	24	0
9	EtOH	12	92
10	MeOH	12	84
11	THF	12	88

[a] Without $AlCl_3$.
[b] 25% of 2,2-bis(indol-3-yl)propane was isolated.



Scheme 1. A proposed mechanism for the reaction of **1a** and **2a** catalyzed by $AlCl_3$.

Table 3
The reaction of heteroaryls **1** and α,β-enals or enones **2** in the presence of $AlCl_3$ in CH_3CN

Entry	Heteroaryl **1**	α,β-Enal or enone **2**	1,1,3-Triheteroaryl **3**	Time (min)	Isolated yield (%)
1	**1a**	**2b**	**3b**	13	90
2	**1b**	**2b**	**3c**	10	88
3	**1c**	**2b**	**3d**	10	97

(*continued on next page*)

Table 3 (*continued*)

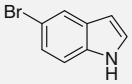
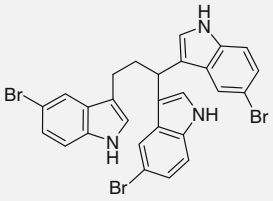
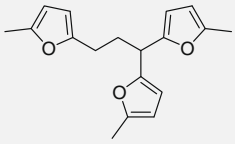
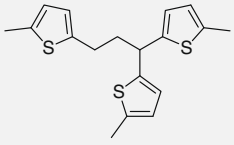
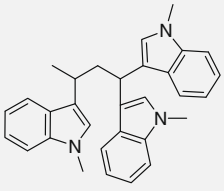
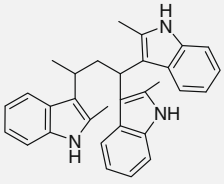
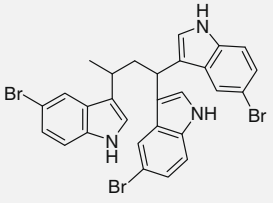
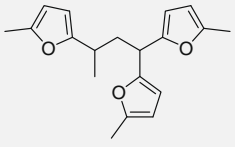
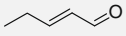
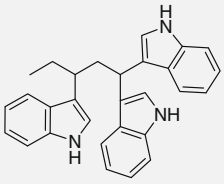
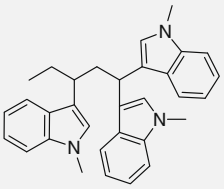
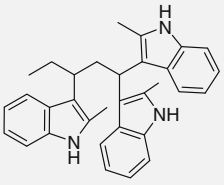
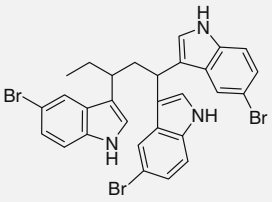
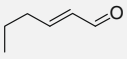
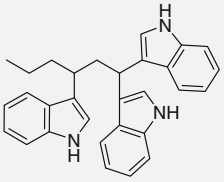
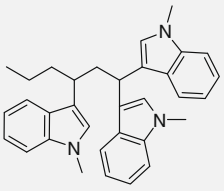
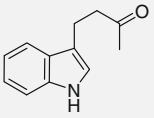
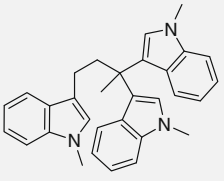
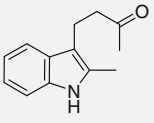
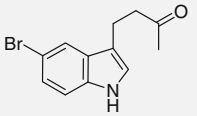
Entry	Heteroaryl **1**	α,β-Enal or enone **2**	1,1,3-Triheteroaryl **3**	Time (min)	Isolated yield (%)
4	 **1d**	**2b**	 **3e**	4 h	96
5	 **1e**	**2b**	 **3f**	4 h	81
6	 **1f**	**2b**	 **3g**	4 h	85
7	**1b**	**2a**	 **3h**	5	97
8	**1c**	**2a**	 **3i**	5	98
9	**1d**	**2a**	 **3j**	2.5 h	98
10	**1e**	**2a**	 **3k**	4 h	92
11	**1a**	 **2c**	 **3l**	1.3 h	96

Table 3 (*continued*)

Entry	Heteroaryl **1**	α,β-Enal or enone **2**	1,1,3-Triheteroaryl **3**	Time (min)	Isolated yield (%)
12	**1b**	**2c**	 **3m**	10	90
13	**1c**	**2c**	 **3n**	5	97
14	**1d**	**2c**	 **3o**	3.25 h	97
15	**1a**	 **2d**	 **3p**	30	100
16	**1b**	**2d**	 **3q**	20	89
17	**1a**	 **2f**	 **3r**	15	92
18	**1b**	**2f**	 **3s**	12 h	70
19	**1c**	**2f**	 **3t**	5	99

(*continued on next page*)

Table 3 (*continued*)

Entry	Heteroaryl **1**	α,β-Enal or enone **2**	1,1,3-Triheteroaryl **3**	Time (min)	Isolated yield (%)
20	**1d**	**2f**	 **3u**	7	100

(except for *n*-hexane) the reaction proceeded smoothly. These experiments revealed that CH_3CN was the best solvent for this reaction (Table 2, entry 1).

A plausible mechanistic pathway is shown in Scheme 1. Although we do not have additional evidence for this, we hypothesize that rapid formation of **3a** may be due to the initial formation of intermediate **A** from $AlCl_3$ and **2a**. Next, indole is added to labile intermediate **A** to yield the corresponding Michael adduct. Subsequent Friedel–Crafts reaction of indole with the aldehydes (twice) gives **3a** (Scheme 1). It is thought that $AlCl_3$ promotes the reaction by increasing the electrophilic character of the enal.

Next, the scope of this catalytic tandem Michael and Friedel–Crafts alkylation was broadened to include the reaction between active heteroaryls with α,β-enals and enones, under the optimized reaction conditions (Table 3).[13] A number of indoles **1a–d** were utilized in the reaction with acrolein (**2b**) catalyzed by $AlCl_3$ in CH_3CN. The reaction afforded the corresponding 1,1,3-triindolyl products **3b–e** in high yields (Table 3, entries 1–4).

It was found that acrolein also reacted efficiently with other heterocycles such as 2-methylfuran and 2-methylthiophene (Table 3, entries 5 and 6). Reaction of other enals such as crotonaldehyde (**2a**), *trans*-2-pentanal (**2c**) and *trans*-2-hexanal (**2d**) with heterocycles **1a–e**, gave a library of 1,1,3-triheteroaryl compounds in high yields (Table 3, entries 7–16).

Reaction of methyl vinyl ketone with indole, 2-methylindole or 5-bromoindole under the same conditions gave only the Michael products (Table 3, entries 17, 19 and 20) even after stirring for 12 h. However, with 1-methylindole (**1b**) the corresponding trisindolyl product **3s** was obtained (Table 3, entry 18).

In conclusion, we have developed a novel and highly efficient method for preparing a library of 1,1,3-triindolyl compounds in excellent yields through the tandem Michael addition and Friedel–Crafts reaction of α,β-unsaturated aldehydes or ketones and indoles, in the presence of a catalytic amount of $AlCl_3$ in CH_3CN. In addition, this system also works well with 2-methylfuran and 2-methylthiophene. Further studies in this area are ongoing.

Acknowledgements

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Supplementary data

Supplementary data (data for other products and copies of spectra) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.10.127.

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12. Shirini, F.; Zolfigol, M. A.; Salehi, P.; Abedini, M. *Curr. Org. Chem.* **2008**, *12*, 183–202.
13. *Typical experimental procedure for the preparation of* **3a**: To a stirring solution of crotonaldehyde (1 mmol) and indole (4 mmol) in CH_3CN (5 mL), $AlCl_3$ (0.1 mmol) was added at room temperature. After 8 min, the solvent was evaporated under reduced pressure. The product was purified by flash column chromatography using *n*-hexane–ethyl acetate (8:2) as eluent to give **3a**[5] in 96% yield; mp 114–116 °C. FT-IR (KBr): 3409, 3053, 2956, 2924, 2867, 1617, 1546, 1455, 1337, 1221, 1094, 1010, 742 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$), δ (ppm): 1.45 (3H, d, J = 6.8 Hz), 2.50 (1H, m), 2.73 (1H, m), 3.10 (1H, m), 4.58 (1H, t, J = 7.3 Hz), 6.85 (1H, s), 6.88 (1H, s), 6.94 (1H, s), 7.01 (3H, m), 7.18 (3H, m), 7.28 (3H, m), 7.47 (2H, t, J = 7.8 Hz), 7.60 (1H, d, J = 7.8 Hz), 7.75 (2H, s, N–H, D_2O exchangeable), 7.80 (1H, s, N–H, D_2O exchangeable). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 21.9, 29.94, 31.9, 43.6, 111.0, 111.12, 111.16, 118.90, 118.97, 119.7, 119.82, 120.2, 120.3, 121.5, 121.7, 122.5, 126.8, 127.0, 136.52, 136.56, 136.62.