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Indium trifluoromethanesulfonate ($In(OTf)_3$). A novel reusable catalyst for intramolecular Diels–Alder reactions

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Abstract

Indium trifluoromethanesulfonate ($In(OTf)_3$) is found to be an effective catalyst for intramolecular Diels–Alder reactions of furans. This novel catalyst, soluble in both aqueous and organic media, is easily recovered from the aqueous layer after the reaction is completed. © 2000 Elsevier Science Ltd. All rights reserved.

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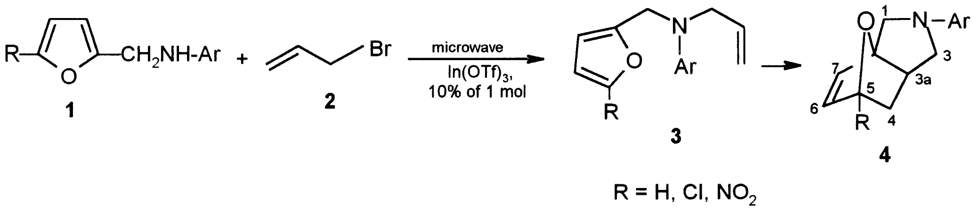
In recent years organic chemistry has witnessed the increased use of indium reagents.[1] It was found that the low reactivity of trivalent organoindium reagents can be increased by complex formation with organolithium compounds.[2] The tetra-organo-indates thus prepared are sufficiently reactive to take part in reactions at ambient temperature.[2a] Allylic indates react with imides and nitriles regioselectively at the γ-carbon to give homoallylamines.[2b] Also indium metal[3] has been found to be an effective reducing agent and indium(III) halide complexes act[4a] as efficient Lewis acid catalysts in Mukaiyama aldol reactions, Friedel–Crafts acylations,[3] Diels–Alder reactions[4b] in water and hetero Diels–Alder cycloadditions.[4c] Our interest in catalytic carbon–carbon bond formation[5] prompted us to investigate the use of indium in



Scheme 1.

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cycloaddition reactions (Scheme 1 and Table 1). In recent years indium triflates have received increasing attention both as reagents and catalysts for organic reactions.[6] These triflates have been shown to be effective, water tolerant, Lewis acids in several carbon–carbon bond forming reactions and in some cases the presence of water even improves their activity. Herein, we report a novel catalyst, indium triflate, for intramolecular Diels–Alder reactions of furans.

Table 1
Reuse of the catalyst

Entry	Run	Product	Yield (%)
1	1st	**4a**	85
2	2nd	**4a**	83
3	3rd	**4a**	80

The (2-furfuryl)aniline[7] **1** (R = H, Ar = Ph) was mixed with allyl bromide and a catalytic amount of indium trifluoromethanesulfonate in an Erlenmeyer flask and irradiated using microwaves for 8 min (Table 2). After the usual work-up, the corresponding IMDA product **4a** was obtained in 85% yield, mp 120–121°C, along with the acyclic product **3a** as a light yellow oil in 10% yield. The diagnostic signal for the furan proton H-1, which was present at δ 7.10 in the ^{1}H NMR spectrum of **1**, was absent in the spectrum of the cycloadduct, whilst the upfield shift of this proton to δ 5.07 showed that cycloaddition had occurred to the furan ring. It is worth mentioning here that this type of IMDA reaction has been reported earlier by Bilovic et al.[8] in which (2-furfuryl)aniline was allowed to react with allyl iodide and the resulting crystalline hydroiodide salt was treated with sodium hydroxide to give oily allyl(2-furfuryl)aniline **3a** in 51% yield. On standing for several days, the oily amine **3a** began to crystallize and was transformed into the corresponding epoxyisoindoline **4a**. Also, it is reported that the IMDA product **4** can undergo retro Diels–Alder reaction on distillation. In contrast to this report, indium triflate completes the reaction within 8–10 min giving excellent yields of the IMDA product in solvent-free conditions.[9] The reaction is less effective when carried out under thermal conditions and takes about 25–30 min giving 40–45% yields. To check the role of HBr formed, a control experiment was performed without using In(OTf)$_3$ under microwave activation. It was observed that when irradiated for 20 min, a mixture of linear **3a** (20%) and IMDA **4a** (6–8%) products was formed. Increasing the reaction time further had no significant effect on the yield and resulted in decomposition, which rules out the participation of the HBr formed in the course of the reaction as catalyst. Moreover, the formation of HBr salt was not detected, probably due to the fact that the excess of allyl bromide removed the HBr from the mixture. When prenyl bromide was used in place of allyl bromide and the mixture irradiated for 20 min no IMDA products were obtained. However, the corresponding linear products were obtained in 25% yield. Interestingly, when thiophene analogues of **1** were used, only *N*-allylation could be observed and no IMDA products were formed.

To include an example of a tricyclic epoxyisoindoline, we have carried out the reaction of furfuryl-*N*-*p*-toluidine with cyclohexenyl bromide in the presence of a catalytic amount of indium triflate under microwave irradiation in the solid state.[10] Here, the reaction proceeds similarly and affords a mixture of acyclic and cyclic products in 20 and 22% yields, respectively, when irradiated for 8 min (Scheme 2). The epoxyisoindoline thus obtained, upon attempted recrystallization in benzene at 80°C, suffers a retro Diels–Alder reaction. To improve the yield,

Table 2

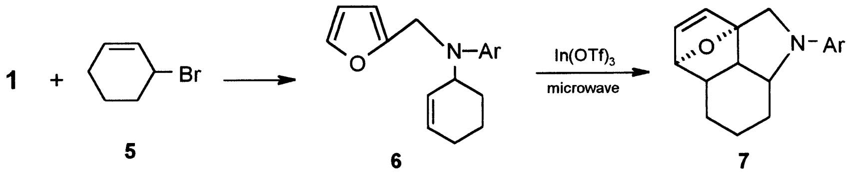
In(OTf)$_3$ catalyzed intramolecular Diels–Alder reaction under microwave activation

Entry	Compound no.	Ar	R	Reaction time, min microwave	Reaction time, min thermal	Mp (°C)	Yield (%) thermal **4**	Yield[a] (%) microwave **4**	Yield[b] (%) microwave **3**
1	**4a**	C_6H_5	H	8	25	120–121	40	85	10
2	**4b**	C_6H_4Cl-*p*	H	9	30	118–120	45	80	10
3	**4c**	C_6H_4Cl-*m*	H	8	30	83–84	40	82	8
4	**4d**	$C_6H_4OC_2H_5$-*p*	H	10	28	97–99	40	85	10
5	**4e**	$C_6H_4OCH_3$-*p*	H	9	25	138–139	45	90	10
6	**4f**	$C_6H_4CH_3$-*p*	H	8	30	108–110	45	80	12
7	**4g**	C_6H_4Br-*p*	H	8	25	129–130	40	80	10
8	**4h**	$C_6H_4OCH_3$-*m*	H	9	30	125–126	42	82	10
9	**4i**	$C_6H_4CH_3$-*m*	H	10	25	121–122	45	82	12
10	**4j**	$C_6H_4CH_3$-*p*	NO_2	10	30	162–163	40	80	10
11	**4k**	$C_6H_4CH_3$-*p*	Cl	8	25	149–150	45	80	10

[a] All the yields refer to isolated chromatographically pure compounds.

[b] Epoxyisoindolines identified by spectral comparison with independently prepared authentic samples.

the acyclic product was first prepared by reacting furfuryl-*N*-*p*-toluidine with cyclohexenyl bromide in the presence of potassium carbonate and TBAB. It was separated and then cyclized under microwave irradiation in the presence of In(OTf)$_3$. After 20 min of irradiation it gave only 15% of the IMDA products and further increasing of reaction time affords only the decomposition products. The advantage of In(OTf)$_3$ as a Lewis acid catalyst is that it can be easily recovered and reused. After the reaction is completed and the IMDA adduct is extracted with dichloromethane, the aqueous layer is concentrated to remove the water under reduced pressure. In(OTf)$_3$ is almost quantitatively recovered and the recovered catalyst is also effective in the IMDA reaction. It should be noted that the yield of second and even third runs are comparable to that of first run.



Scheme 2.

Therefore, this new method using indium triflate under microwave activation has the following advantages: (a) The reaction is complete in a few minutes affording high yields of IMDA products; (b) Instead of isolating salts the reaction proceeds in one-step; and (c) The catalyst can be recovered and reused. We believe this reaction offers considerable synthetic potential because of the two following reasons. Firstly, transformation of the furan to an indole derivative by cleavage of epoxy bridge of the adduct and concomitant aromatization and, secondly, the availability of a large number of functionalized furans. Further investigations to develop synthetic techniques, especially carbon–carbon bond forming reactions using this novel reusable catalyst are now in progress.

Acknowledgements

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9. In a typical procedure, (2-furfuryl)aniline (1.73 g, 10 mmol), allyl bromide (2.42 g, 20 mmol) and indium triflate (60 mg, 0.1 mmol) were mixed together without solvent in an Erlenmeyer flask and placed in a commercial microwave oven (operating at a frequency of 2450 MHz). The reaction mixture was irradiated for 8 min (monitored by TLC) and after completion it was allowed to cool to room temperature, washed with water and extracted with CH_2Cl_2 (2×30 ml) and dried over anhydrous sodium sulfate. Removal of solvent and the residue on purification by column chromatography using petroleum ether/$CHCl_3$ (4:1) as eluent, affords the corresponding IMDA product *N*-phenyl-4*H*-5,7*a*-epoxyisoindoline **4a**, mp 120–21°C, in 85% yield (entry 1) along with the acyclic product allyl(2-furfuryl)aniline **3a** (light yellow oil) in 10% yield. Similar treatment of other furfuryl-*N*-arylamines **1b–k** affords the corresponding IMDA products **4b–k** in 80–90% yields. These products were fully characterized by spectroscopic data and finally by comparison with authentic samples. Spectroscopic data of **4a** [*N*-(phenyl)-5,7*a*-epoxy-4*H*-isoindoline (Ar = Ph R = H)]. IR (KBr, cm^{-1}): 2995, 2825, 1650, 1575. MS *m*/*z*: 213 (M^+). ^1H NMR (300 MHz, $CDCl_3$): δ 1.46 (dd, $J = 7.6$ and 11.6 Hz, 1H, 4-H), 1.84 (m, 1H, 3a-H), 2.18 (m, 1H, 4-H), 2.93 (t, $J = 9$ Hz, 1H, 3-H), 3.00 (d, $J = 11.4$ Hz, 1H, 1-H), 3.75 (t, $J = 9$ Hz, 1H, 3-H), 3.91 (d, $J = 11.4$ Hz, 1H, 1-H), 5.07 (dd, $J = 1.6$ and 4.4 Hz, 1H, 5-H), 6.39–6.70 (m, 5H, ArH), 7.18 (m, 1H, 6-H), 7.24 (d, $J = 2$ Hz, 1H, 7-H). Anal. calcd for $C_{14}H_{15}NO$: C, 78.87; H, 7.04; N, 6.57. Found: C, 78.61; H, 6.90; N, 6.65. Similarly, cyclohexenyl bromide **5** was reacted with **1** (R = H, Ar = $C_6H_4CH_3$-*p*) and the corresponding acyclic **6** and cyclic **7** products were isolated in 20 and 22% yields, respectively.
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