InCl₃-SiO₂ Catalyzed Electrophilic Amination of Arenes: A Facile and Rapid Synthesis of Aryl Hydrazides¹

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Abstract: Electron-rich arenes undergo electrophilic amination with diethyl azodicarboxylate on the surface of silica gel impregnated with indium trichloride in solvent-free conditions to afford *para*-substituted aryl hydrazides. Improved yields and enhanced rates are obtained by employing microwave irradiation.

Key words: InCl₃-SiO₂, arenes, aryl hydrazides, microwaves.

Aryl hydrazides are versatile intermediates for the synthesis of aromatic amines² and aryl hydrazines.³ Aromatic amines exhibit a wide spectrum of biological activities⁴ such as antibiotics, analgesics and β -adrenergic blockers. In addition, aromatic amines are the key intermediates for the synthesis of a variety of aromatic compounds via diazotization and nucleophilic substitution reactions. Aryl hydrazines are important precursors for the synthesis of a variety of heterocycles⁵ such as indoles, pyrazoles, β -lactams, quinazolines and many others, which are known to be biologically active. Aryl hydrazides can be prepared by the condensation of aryl lithium or aryl magnesium reagents with di-t-butyl azodicarboxylate⁶ and also by the electrophilic amination of electron-rich arenes with bis(2,2,2-trichloroethyl)azodicarboxylate under thermal or Lewis acid catalysis.^{7,8} A thermal or acid catalyzed electrophilic amination typically requires high temperature or strongly acidic conditions and the highly reactive bis(trichloroethyl)azodicarboxylate to promote the amination reaction. Further, many of these procedures are of limited synthetic scope due to lower yields, poor regioselectivity, extended reaction time, high temperature and the amount of the catalyst or solvent used. However, there is no report on the synthesis of aryl hydrazides from arenes and diethyl azodicarboxylate using indium halides. Therefore, the development of new methods that lead to convenient procedures and better yields are of interest. In recent years, there has been increasing interest on solid supported reagents coupled with microwave irradiation⁹ due to the benefits of enhanced reaction rates, improved yields, cleaner reaction profiles, greater selectivity and operational simplicity.

In continuation of our interest on surface mediated solid state reactions coupled with microwave irradiation,¹⁰ herein we report an efficient and rapid method for the syn-

thesis of aryl hydrazides through the electrophilic amination of electron rich arenes with diethyl azodicarboxylate using indium trichloride supported on SiO_2^{11} in solventfree conditions.

$$R + EtOOC-N=N-COOEt \xrightarrow{InCl_3-SiO_2} R + \underbrace{From N-COOEt}_{NHCOOEt}$$

Scheme

Aryl hydrazides were formed in high yields in a short reaction time when the reactants were admixed with InCl₃-SiO₂ in Erlenmeyer flask and exposed to microwave irradiation at 450 W using BPL, BMO-700 T focused microwave oven (Scheme). The reactions were clean and completed in 2-6 min with high regioselectivity. The less reactive substrates like anisole, naphthalene, 3,4dimethoxybromobenzene, 1,4-dimethoxybenzene and xylene smoothly underwent electrophilic amination to afford corresponding hydrazides in good yields under microwave irradiation. The electrophilic amination reaction of arenes with diethyl azodicarboxylate in the presence of $BF_3 \cdot OEt_2$ or CF_3SO_3H , or TFA resulted in a complex mixture of products and also the amination was much slower using LiClO₄ as a catalyst compared to reactions carried out in the presence of indium trichloride-SiO₂ under microwave irradiation. The reaction rates and yields were dramatically enhanced by microwave irradiation. This is due to the more absorption of microwave energy by the polar media as well as polar reactants, which generates heat energy as required to promote the amination reaction. The reaction is highly regioselective, affording high yields of products in a short reaction time.

The present study has unequivocally confirmed that the conventional heating in 1,2-dichloroethane and longer reaction times (8-22 h) required for the amination of arenes are improved using microwave irradiation, which is becoming an alternate and substitute heating source. For example, the treatment of 1,2-dimethoxybenzene with diethyl azodicarboxylate in the presence of indium trichloride-SiO₂ (3 wt equiv of arene) under microwave irradiation at 450 watts for 3 min gave the corresponding hydrazide in 88% yield after filtration through a small silica gel column, whereas under conventional heating conditions, the hydrazide was obtained in 75% yield after 10 h of heating in 1,2-dichloroethane¹² (Table, entry, a). Invariably, the products obtained by microwave irradiation were purified with more ease. The hydrazides thus ob-

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Table Indium(III)Chloride-SiO₂ Catalyzed Electrophilic Amination of Arenes with DEAD.

Entry	Arene	Hydrazide ^a	Microwave ^b Time (Yield)	Conventional Heating ^c Time (Yield)
a	MeO	MeO N-COOE: NHCOOE:	3 min (88)	10 h (75)
b	MeO MeO	MeO NHCOOEt MeO	2 min (92)	8 h (80)
с	OMe OMe	OMe OMe N=COOEt NHCOOEt	3 min (87)	12 h (70)
d		Meo OMe I NHCOOEt	3 min (81)	15 h (68)
e	OMe	OMe N-COOEt NHCOOEt	3 min (85)	10 h (73)
f	OMe		2 min (90)	8 h (78)
g	MeO UMe	MeO OMe MeO N=COOEt NHCOOEt Pr	6 min (83)	14 h (71)
h	OMe		3 min (87)	12 h (78)
i	OMe	NHCOOE: NCOOE: OMe	3 min (90)	12 h (78)
j	CH ₃	NHCOOEt NCOOEt CH3	4 min (72)	20 h (65)
k	\bigcirc	N-COOEt NHCOOEt	6 min (78)	22 h (62)
1			6 min (75)	15 h (71)

^a All products were characterized by ¹H NMR, IR and Mass spectra.^{12,} ^b Microwave irradiation was carried out at 450 W (BPL, BMO 700 T).

MeO

ЦC

COOE . NHCOOEt

^c Conventional heating in 1,2-dichloroethane.

MeO

ЦC

m

tained were easily converted to their corresponding anilines by reducing with zinc in acetic acid.

In conclusion, the method describes a rapid and efficient procedure for the preparation of aryl hydrazides through the electrophilic amination of arenes with diethyl azodicarboxylate catalyzed by indium trichloride supported on silica gel in solvent-free conditions. The procedure offers several advantages including mild reaction conditions, cleaner reaction profiles, high regioselectivity, short reaction times, high yields of aminated products and simple experimental / product isolation procedures which makes it a useful and attractive alternative process for acid sensitive molecules where nitration conditions are unsuitable.

22 h (60)

6 min (68)

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- (11) The catalyst (InCl₃-SiO₂) was prepared by adding silica gel
 (2 g , Aldrich, 230-400 mesh) to a stirred solution of InCl₃
 (0.3 mmol) in acetonitirle (2 mL) followed by evaporation of solvent in vacuo.
- (12) (a) Microwave irradiation: 1,2-Dimethoxybenzene (5 mmol), diethyl azodicarboxylate (5 mmol) and InCl₃-SiO₂ (3 wt equiv of arene) were admixed in Erlenmeyer flask and exposed to microwave irradiation at 450 watts using BPL, BMO-700 T focused microwave oven for 3 min (pulsed irradiation 1 min with 20 s interval). On completion, the reaction mixture was directly charged on a small silica gel column and eluted with a mixture of ethyl acetate-hexane (2:8)to afford pure hydrazide in 88% yield as a pale yellow solid. (b) Conventional method: A mixture of 1,2-dimethoxy benzene (5 mmol), DEAD (5 mmol) and InCl₃ (10 mol%) in 1,2- dichloroethane (10 mL) was stirred at reflux for 10 h. On completion, the reaction mass was diluted with H₂Oand extracted with $CHCl_3$ (2 × 15 mL). The organic layers were dried over anhydrous Na₂SO₄ and purified by column chromatography to afford pure hydrazide in 75% yield as pale yellow solid. mp 108-110 °C, IR(KBr): 3280, 2990, 1741, 1709, 1529, 1248, 1023 cm⁻¹. ¹H NMR (CDCl₃)δ: 1.25 (t, 6 H, J = 6.8 Hz), 3.80 (s, 6 H), 4.20 (q, 4 H, J = 6.8 Hz), 6.80 (d, 1 H, J = 8.0 Hz), 6.9 (dd, 1 H, J = 8.0 and 2.4 Hz), 6.95 (d, 1 H, J = 2.4 Hz), 7.05 (brs, 1 H, NH). EIMS (m/ z)(%): 312(80)M⁺, 240(50), 225(30), 179(10), 167(100), 138(40), 77(20).