

Sc(OTf)₃ Catalyzed Electrophilic Amination of Arenes: An Expedient Synthesis of Aryl Hydrazides

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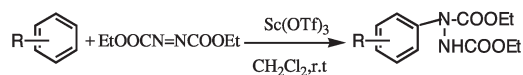
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Arenes react smoothly with diethyl azodicarboxylate in the presence of a catalytic amount of scandium triflate in dichloromethane at ambient temperature to afford the corresponding aryl hydrazides in high yields with high regioselectivity.

Aryl hydrazides are important precursors for the synthesis of a variety of heterocycles¹ such as indoles, pyrazoles, β -lactams, quinazolines and many others, which are known to be biologically active. In addition, they can be easily transformed to aryl amines² and aryl hydrazines.³ Generally, aryl hydrazides are prepared by the condensation of aryl lithium or aryl magnesium reagents with di-*t*-butyl azodicarboxylate⁴ and also by the electrophilic amination of electron rich arenes with bis(2,2,2-trichloroethyl) azodicarboxylate under thermal or Lewis acid catalysis.^{5,6} A thermal or acid catalyzed electrophilic amination typically requires high temperature or strongly acidic conditions and the highly reactive electrophile bis(trichloroethyl) azodicarboxylate to promote the reaction. However, many of these procedures have limitations in one way or other thereby restricting their wide spread applicability. Thus, high acidity, high reaction temperature, prolonged reaction time, critical handling of catalysts, unsatisfactory yields, poor regioselectivity and non-catalytic nature of the reagents are unfavorable factors. Therefore, the development of new reagents that are more efficient and lead to convenient procedures and better yields are desirable. Moreover, no attempt has been made to recycle the catalyst, thereby making the process more eco-friendly. Metal triflates are unique Lewis acids that are currently of great research interest.⁷ Particularly, scandium salts are attractive because they are quite stable to water and reusable and in addition they are highly effective for the activation of nitrogen containing compounds. Therefore, scandium triflate is an efficient catalyst compared to traditional Lewis acids in several carbon-carbon bond forming reactions and have found wide applications in organic synthesis.⁸

In this report, we wish to highlight our results on the electrophilic amination of arenes with diethyl azodicarboxylate using catalytic amount of scandium triflate (Scheme 1).



Scheme 1.

The treatment of anisole with diethyl azodicarboxylate (DEAD) in the presence of 5 mol% Sc(OTf)₃ at ambient temperature resulted in the formation of *p*-anisyl hydrazide in 90% yield. Similarly, several arenes reacted smoothly with diethyl azodicarboxylate to give the corresponding aryl hydrazides in high yields.⁹ The method is clean and highly regioselective. The extent of electron density and the nature of the substituent on the aromatic ring show some effect on this conversion. Hydroxy

substituted benzenes i.e. phenols reacted rapidly with diethyl azodicarboxylate to afford the respective aryl hydrazides in excellent yields. The activated arenes such as anisole, veratrole, 1,2-methylenedioxybenzene and 1,3,5-trimethoxybenzene also gave the corresponding aryl hydrazides in high yields in a short reaction time. In all cases, the reactions proceeded smoothly at ambient temperature with high regioselectivity. However, unactivated arenes such as benzene, toluene, naphthalene, anthracene and xylene took longer reaction time to achieve

Table 1. Sc(OTf)₃ catalyzed electrophilic amination of arenes with DEAD

Entry	Arene	Hydrazide ^a	Sc(OTf) ₃	
			Time	Yield (%) ^b
a.			1.5 h	90
b.			2.0 h	88
c.			1.5 h	92
d.			1.5 h	85
e.			3.0 h	80
f.			2.5 h	94
g.			6.5 h	68
h.			2.0 h	85
i.			1.5 h	82
j.			20 min	95
k.			35 min	87
l.			15 min	93
m.			2.5 h	90
n.			3.5 h	78
o.			4.0 h	85
p.			4.5 h	82

^aAll products were characterized by ¹H NMR, ¹³C NMR, IR and mass spectroscopy. ^bIsolated and unoptimized yields.

yields comparable with those of their electron rich counterparts. Particularly, benzene and toluene afforded 48% and 53% yields respectively in the presence of 5 mol% $\text{Sc}(\text{OTf})_3$ at their refluxing temperature for 12 h. Similar yields and selectivity were also obtained with 5 mol% $\text{In}(\text{OTf})_3$ under the same reaction conditions (Table 2). However, in the absence of catalyst, the reaction did not yield any product even at reflux temperature. The lowering of the reaction temperature was detrimental to the efficiency of this procedure. The scope of scandium triflate catalyzed electrophilic amination of arenes was investigated with respect to the activated and unactivated aromatics illustrated in Table 1. Scandium triflate was found to be the best catalyst for the amination of activated arenes with DEAD and surprisingly, the only catalyst effective for the amination of unactivated aromatics, albeit, requiring longer reaction times (2.5–4.5 h) to achieve complete conversion. Another advantage of this procedure is that scandium triflate was recovered from aqueous layer during the

work-up and reused in subsequent reactions with gradual decrease in activity; for example, the reaction of anisole with diethyl azodicarboxylate gave the corresponding *p*-anisyl hydrazide in 90%, 85% and 80% yield over three cycles.

In summary, we have demonstrated that $\text{Sc}(\text{OTf})_3$ is an efficient and reusable Lewis acid for the electrophilic amination of arenes with diethyl azodicarboxylate. In addition to its efficiency, simplicity, and milder reaction conditions, this method provides excellent yields of products with high regioselectivity. This procedure is very useful for acid sensitive molecules where nitration conditions are unsuitable.

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- 9 Experimental Procedure: A mixture of arene (5 mmol), diethyl azodicarboxylate (5 mmol), scandium triflate or indium triflate (5 mol%) in dichloromethane (10 mL) was stirred at ambient temperature for an appropriate time (Table 1 and 2). After completion of the reaction as indicated by TLC, the reaction mixture was diluted with water and extracted with dichloromethane (2×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 , concentrated *in vacuo* and purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate-hexane, 2 : 8) to afford pure aryl hydrazide. **2b** (Table 1): Solid, m.p. 110 °C, ^1H NMR (CDCl_3) δ : 1.25 (t, 6H, $J = 6.8$ Hz), 3.80 (s, 6H), 4.20 (q, 4H, $J = 7.0$ Hz), 6.70 (d, 1H, $J = 8.0$ Hz), 6.85 (d, 1H, $J = 8.0$ Hz), 6.94 (s, 1H), 7.20 (brs, NH). ^{13}C NMR (CDCl_3 , proton decoupled) δ : 14.3, 29.5, 55.8, 62.1, 62.7, 109.4, 110.7, 117.3, 134.9, 147.7, 148.7, 155.1, 156.2. IR (KBr) ν : 3345, 3030, 2970, 1740, 1520, 1285, 1038, 790. EIMS: m/z : M^+ , 312, 240, 167, 141, 104, 83, 65, 43. **2n** (Table 1): Solid, m.p. 137 °C, ^1H NMR (CDCl_3) δ : 1.25 (t, 3H, $J = 7.0$ Hz), 1.30 (t, 3H, $J = 7.0$ Hz), 4.25 (q, 4H, $J = 7.2$ Hz), 7.25 (brs, NH), 7.45–7.55 (m, 4H), 7.80–7.90 (m, 2H), 7.95 (d, 1H, $J = 8.0$ Hz). ^{13}C NMR (CDCl_3 , proton decoupled) δ : 14.3, 18.3, 22.0, 62.0, 62.9, 121.3, 122.9, 124.6, 125.3, 126.8, 127.9, 128.4, 128.6, 128.8, 130.5, 156.4. IR (KBr) ν : 3350, 3029, 2978, 1720, 1520, 1250, 1070, 795. EIMS: m/z : M^+ , 302, 229, 199, 115, 83, 43. **2o** (Table 1): Solid, m.p. 163 °C, ^1H NMR (CDCl_3) δ : 1.15 (t, 3H, $J = 7.0$ Hz), 1.30 (t, 3H, $J = 7.0$ Hz), 2.58 (s, 3H), 4.20 (q, 4H, $J = 7.2$ Hz), 6.98 (brs, NH), 7.18–7.63 (m, 4H), 7.78–8.0 (m, 2H). ^{13}C NMR (CDCl_3 , proton decoupled) δ : 14.3, 18.3, 22.0, 62.0, 62.9, 121.3, 122.9, 124.6, 125.3, 126.8, 127.9, 128.4, 128.6, 128.8, 130.5, 156.4. IR (KBr) ν : 3348, 3027, 2975, 1745, 1525, 1280, 1040, 793. EIMS: m/z : M^+ , 316, 243, 171, 115, 83, 43.

Table 2. $\text{In}(\text{OTf})_3$ catalyzed electrophilic amination of arenes with DEAD

Entry	Arene	Hydrazide ^a	$\text{In}(\text{OTf})_3$	
			Time	Yield (%) ^b
a.			2.5 h	85
b.			3.5 h	80
c.			3.0 h	90
d.			3.5 h	81
e.			4.0 h	78
f.			3.5 h	89
g.			3.0 h	83
h.			2.5 h	75
i.			1.0 h	90
j.			1.5 h	85
k.			1.0 h	87
l.			3.0 h	83
m.			6.0 h	70
n.			5.0 h	75
o.			7.0 h	68

^aAll products were characterized by ^1H NMR, ^{13}C NMR, IR and mass spectroscopy. ^bIsolated and unoptimized yields.