Tetrahedron Letters 54 (2013) 530–532

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Ruthenium chloride, a new and efficient catalyst for direct amination of arenes with azodicarboxylates

Suleman M. Inamdar [a], Vinod K. More [a], Sisir K. Mandal [b,*]

[a] Aditya Birla Science & Technology Centre, Plot No. 1 & 1-A/1, MIDC Taloja, Panvel, Navi Mumbai 410 208, India
[b] Technology Platform Department, Asian Paints R & T Centre, Plot No. C3-B/1, TTC Industrial Area, Pawane, Thane Belapur Road, Navi Mumbai 400 705, India

ARTICLE INFO

Article history:
Received 6 June 2012
Revised 17 November 2012
Accepted 20 November 2012
Available online 27 November 2012

Keywords:
Ruthenium chloride
Amination
Arene
Azodicarboxylate

ABSTRACT

An efficient cross coupling amination of arene with azodicarboxylate to afford hydrazides catalysed by ruthenium chloride has been demonstrated. The catalyst was found to be effective across a spectrum of arenes with a variety of functional groups. The yields are found to be modest to low depending on the type of substrates. The catalyst can be recycled in ligand free conditions to afford the cross coupling reaction.

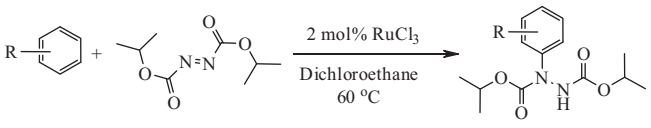
Derivatives of aromatic amines are known to be biologically active and have found applications in antibiotics,[1] analgesics[2] and R-adrenergic blockers.[3] Monosubstituted hydrazines are also intermediates in the preparation of heterocyclic compounds such as pyrazoles,[4] indazoles,[5] imidazolinones[6] and cinnolines.[7] Moreover, 2-heteroaryl hydrazines[8] are interesting synthetic targets due to their efficiency as ligands for a variety of metal complexes.[9–11] Traditionally, aryl hydrazides were prepared by treating azodicarboxylates with either an aryl lithium or an aryl magnesium halide.[12] Diprotected aryl hydrazines are generally prepared by electrophilic amination[13] of electron-rich arenes using dialkyl azodicarboxylates or via the reaction of *tert*-butyl carbazates with boronic acids catalysed by cuprous chloride at room temperature.[14]

Reactions of electron rich arenes with azodicarboxylate in the presence of various acids and metal halides are well known.[15–18,13b,19–21] Taking a step forward, gold catalysed amination of electron rich as well as electron poor arenes with better activities has been recently reported by Zhang and co-workers[22] Gold complexes are air sensitive and expensive compared to many other metal complexes. In this respect, there is still a need for improved and more general catalytic processes for arene amination.

Although the reaction was efficiently promoted by the above reagents in the presence of catalysts, they suffer from one or more disadvantages such as use of drastic reaction conditions, poor reactivity of electron deficient arenes and in many cases, the formation of several by-products. In addition, these catalysts are moisture sensitive and cannot be regenerated. This makes the process less environmentally friendly and unattractive for commercialization. Thus, there is still a need of cheaper, recyclable and environmentally friendly catalysts for the direct amination of arenes. Herein, we report a new ruthenium (III) chloride catalysed direct amination of electron rich as well as electron deficient arenes with azodicarboxylates under mild reaction conditions (scheme 1). Catalyst recyclability, recovery and performance of $RuCl_3$ in direct amination of anisole with diisopropyl azodicarboxylate were evaluated.

Initially, the amination reaction between anisole and diisopropyl azodicarboxylate was selected as a model reaction to optimize the reaction conditions using $RuCl_3$ as the catalyst.[23] A preliminary solvent screening indicated that dichloroethane could be the most suitable solvent for the amination reaction (Table 1) among the solvents studied.

In order to understand the effect of catalyst loading, the cross coupling reactions were carried out at different catalyst loading and the data are presented in Table 1. The results show that 2 mol % of $RuCl_3$ loading gives excellent result as compared to



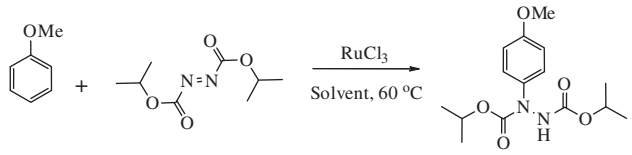
R= Me, OMe, OH, halogen, etc

Scheme 1. $RuCl_3$ catalysed direct amination of arenes with azodicaboxylate.

* Corresponding author.
E-mail address: sisir.mandal@asianpaints.com (S.K. Mandal).

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.11.075

Table 1
Effect of solvent on amination reaction of anisole catalysed by $RuCl_3$[a]



Entry	Solvent	Catalyst loading in mol %	Yield[b] (%)
1	Dichloroethane	1	54
2	Dichloroethane	2	93
3	Dichloroethane	5	91
4	Dichloroethane	10	92
5	Dichloromethane	2	46[c]
6	Methanol	2	73
7	Chloroform	2	70
8	THF	2	64
9	Toluene	2	58
10	Dioxane	2	55
11	CH_3CN	2	76

[a] Reaction conditions: diisopropyl azodicaboxylate (1 mmol), anisole (1.2 mmol), $RuCl_3$ catalyst, solvent (5 ml), 4 h, 60 °C.
[b] Isolated yields.
[c] Reaction perform at room temperature.

1 mol % within the experimental error. There was no improvement in the yield when the catalyst loading was more than 2 mol %.

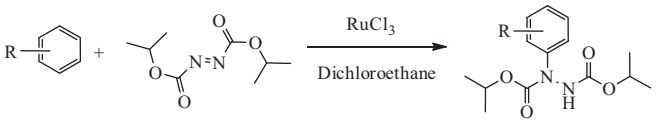
Electronic factors play an important role in the reaction. In order to understand the electronic factors the study was extended to alternatively substituted arenes. Table 2 presents the relevant data. Amination of anisole, phenol and 3-methyl phenol is achieved in excellent yields in the presence of 2 mol % $RuCl_3$ catalyst (Table 2, entries **a–c**). However, the reaction of 2,3,6-trimethylphenol and 2,3-dimethylphenol (Table 2, entries **d–e**) amination was achieved in good yields with long reaction time. In case of 3-amino phenol, durene and mesitylene (Table 2, entries **f–h**) the yield of amination product was moderate even after a longer reaction time and excess amount of catalyst (5 mol %). This low yield probably is due to the crowding on the ring. Electron deficient halo-arenes such as 2-chlorophenol, 3-bromophenol, fluorobenzene, chlorobenzene and 1,3-difluorobenzene (Table 2, entries **i–m**) provided poor yields in long reaction times with 2 mol % $RuCl_3$ catalyst. The results show that the arenes with electron rich substituents give better yields compared to arenes with electron deficient substituents.

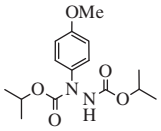
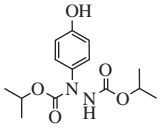
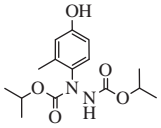
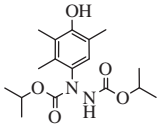
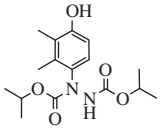
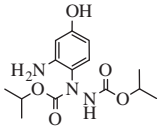
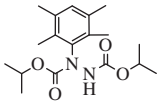
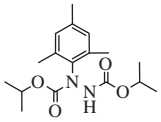
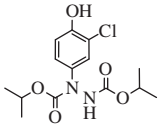
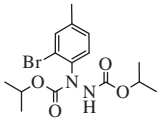
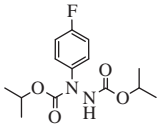
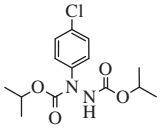
In order to understand the mechanism of the reaction, we performed a series of experiments with anisole and diisopropyl azodicarboxylate using stoichiometric amounts of $RuCl_3$ in deuterated chloroform under dry conditions. In the absence of arene, the ^1H NMR shifts of azodicarboxylates remained unchanged on addition of $RuCl_3$. However, change in ^1H chemical shift was observed from δ 5.16–5.29 ppm to δ 4.85–4.98 ppm when azodicarboxylate was added to the system in the presence of both $RuCl_3$ and arenes. Detailed mechanistic study is in progress.

The reusability of $RuCl_3$ catalyst was studied for the direct amination reaction between anisole with diisopropyl azodicarboxylate in dichloroethane solvent at 60 °C. The results are summarized in Table 3. The catalyst was allowed to settle down in the reaction mixture and subsequently recovered near quantitatively by decantation and reused (Table 3, entries **2–3**) with a little loss of catalytic activity compared to the fresh catalyst. The above results indicate that the synthesis can be carried out with a minimal loss of the catalyst making the method more advantageous and economic. The gradual loss of yield in Table 3 could be due to the loss of catalyst during recovery process in a small scale.

In conclusion, we have developed an inexpensive and efficient method catalysed by $RuCl_3$ for the direct amination across a spec-

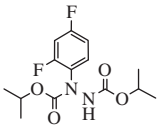
Table 2
$RuCl_3$ catalysed direct amination of arenes[a]



Entry	Arenes	Product	Time (h)	Yield[b]
a			4 12	93 41[c]
b			5	91
c			5	86
d			12	86
e			15	79
f			10	75
g			12	73
h			12	83
i			18	58
j			12	52
k			36	43
l			36	39

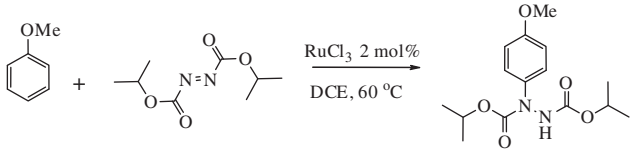
(*continued on next page*)

Table 2 (*continued*)

Entry	Arenes	Product	Time (h)	Yield[b]
m			30	20

[a] Reaction conditions: diisopropyl azodicaboxylate (1 mmol), arene (1.2 mmol), $RuCl_3$ (2 mol %), DCE (5 ml), 60 °C.
[b] Isolated yields.
[c] $RuCl_3{\cdot}3H_2O$ was used as catalyst.

Table 3
$RuCl_3$ catalyst reusability study for the amination reaction[a]



Entry	Time (h)	Yield[b]
1	4	93
2	5	90
3	5	88

[a] Reaction conditions: diisopropyl azodicaboxylate(1 mmol), anisole (1.2 mmol), $RuCl_3$ (2 mol %), DCE (5 ml), 60 °C.
[b] Isolated yields.

trum of arenes with azodicarboxylates in a modest to low yields. The effects of solvent, catalyst loading and the substituents of arenes are studied. The choice of arene is paramount in the selectivity of the reaction. The method of catalyst recovery and its re-use is provided. The protocol used in the synthesis may have a significant advantage over other routes for the synthesis of biologically active heterocyclic compounds.

Acknowledgment

The financial assistance from Indira Gandhi Centre for Atomic Research (IGCAR), Kalpakkam, India is kindly acknowledged.

References and notes

1. (a) Thiericke, R., Jr.; Zeeck, A. J. *Chem. Soc., Perkin Trans.* **1988**, *1*, 2123; (b) Rinehart, K. L.; Shield, L. S. *Fortschr. Chem. Org. Naturst.* **1976**, *33*, 231.
2. Ameer, B.; Greenblatt, D. J. *Ann. Intern. Med* **1977**, *87*, 202.
3. (a) Basil, B.; Jordan, R.; Loveless, A. H.; Maxwell, D. R. *Br. J. Pharmacol.* **1973**, *48*, 98211; (b) Cuthbert, M. F.; Owusu-Ankomah, K. *Br. J. Pharmacol.* **1971**, *43*, 639.
4. Stauffer, S. R.; Haung, Y. R.; Aron, Z. D.; Coletta, C. J.; Sun, J.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. *Bioorg. Med. Chem.* **2001**, *9*, 151.
5. Boudreault, N.; Leblanc, Y. *Org. Synth.* **1996**, *74*, 241.
6. Bozzini, S.; Nitti, R.; Pitacco, G.; Pizzioli, A.; Russo, C. *J. Heterocycl. Chem.* **1966**, *33*, 1217.
7. Wunsch, B.; Nerdinger, S.; Hofner, G. *Liebigs Ann.* **1995**, 1303.
8. Arterburn, J. B.; Rao, K. V.; Ramdas, R. B.; Dible, R. *Org. Lett.* **2001**, *3*, 1351.
9. Alberto, R.; Schibli, R.; Schubiger, A. P.; Abram, U.; Pietzsch, H.-J.; Johannsen, B. *J. Am. Chem. Soc.* **1999**, *121*, 6076.
10. Edwards, D. S.; Liu, S.; Harris, A. R.; Poirier, M. J.; Ewels, B. A. *Bioconjugate Chem.* **1999**, *10*, 803.
11. Rose, D. J.; Maresca, K. P.; Nicholson, T.; Davison, A.; Jones, A. G.; Babich, J.; Fischman, A.; Graham, W.; DeBord, J. R. D.; Zubieta, J. *Inorg. Chem.* **1998**, *37*, 2701.
12. Demers, P.; Klaubert, D. H. *Tetrahedron Lett.* **1987**, *28*, 4933.
13. (a) Bombek, S.; Lenarsic, R.; Kocevar, M.; Saint-Jalmes, L.; Desmurs, J. R.; Polanc, S. *Chem. Commun.* **2002**, 1494; (b) Mitchell, H.; Leblanc, Y. *J. Org. Chem.* **1994**, *59*, 682; (c) Kinart, W. J.; Kinart, C. M. *J. Organomet. Chem.* **2003**, *665*, 233.
14. Kobalka, G. W.; Guchhait, S. K. *Org. Lett.* **2003**, *5*, 4129.
15. (a) Leblanc, Y.; Boudreault, N. *J. Org. Chem.* **1995**, *60*, 4268; (b) Zaltsgendler, I.; Leblanc, Y.; Bernstein, M. A. *Tetrahedron Lett.* **1993**, *34*, 2441; (c) Boudreault, N.; Leblanc, Y. *Org. Synth.* **1997**, *74*, 241; (d) Bombek, S.; Pozgan, F.; Kocevar, M.; Polanc, S. J. *J. Org. Chem.* **2004**, *69*, 2224.
16. (a) Carlin, R. B.; Moores, M. S. *J. Am. Chem. Soc.* **1962**, *84*, 4107; (b) Schroeter, S. H. *J. Org. Chem.* **1969**, *34*, 4012.
17. Yadav, J. S.; Reddy, B. V. S.; Veerendhar, G.; Rao, R. S.; Nagaiah, K. *Chem. Lett.* **2002**, 318.
18. Lee, K. Y.; Im, Y. J.; Kim, T. H.; Kim, J. N. *Bull. Korean Chem. Soc.* **2001**, *22*, 127.
19. Yadav, J. S.; Reddy, B. V. S.; Kumar, G. M.; Madan, C. *Synlett* **2001**, 1781.
20. Lenarsic, R.; Kocevar, M.; Polanc, S. *J. Org. Chem.* **1999**, *64*, 2558.
21. Zaltsgendler, I.; Leblanc, Y.; Bernstein, M. A. *Tetrahedron Lett* **1993**, *34*, 2441.
22. (a) Liuqun, G.; Neo, B. S.; Zhang, Y. *Org. Lett*. **1872**, *2011*, 13; (b) Ackermann, L.; Althammer, A.; Norn, R. *Tetrahedron* **2008**, *64*, 6115.
23. **General procedure for $RuCl_3$ catalysed direct amination reaction of arenes with azodicarboxylate:** Azodicarboxylate (1 mmol), arene (1.2 mmol) and $RuCl_3$ (2 mol %) were stirred in dichloroethane solvent (5 ml) at 60 °C till the reaction is completed (Table 2). The progress of the reaction was monitored by TLC. After the appropriate time (Table 2), the mixture was filtered to recover the catalyst and the filtrate was evaporated under reduced pressure to get crude product. The crude product thus obtained was purified by column chromatography on silica gel using hexane–ethyl acetate (90:10) as eluent to afford the pure product. All products were characterized by ^1H NMR and ^{13}C NMR.
Spectral data for selected compounds. *Diisopropyl 1-(4-methoxyphenyl) hydrazine-1,2-dicarboxylate (Table 2, entry a).* Yield: 93%; ^1H NMR (200 MHz, $CDCl_3$): δ = 1.17–1.22 (dd, 12H), 3.73 (s, 3H), 4.85–5.0(m, 2H), 6.73 (d, 2H), 6.86 (br s, 1H), 7.21 (d, 2H), ^{13}C NMR (200 MHz, $CDCl_3$): δ = 22.06, 55.28, 69.85, 70.52, 113.77, 125.45, 125.73, 126, 126.27, 126.51, 127.38, 135.01, 155.98, 157.99; Anal. Calcd for $C_{15}H_{22}N_2O_5$: C, 58.05; H, 7.15; N, 9.03. Found: C, 58.11; H, 7.13; N, 9.14.
Diisopropyl 1-(4-hydroxyphenyl)hydrazine-1,2-dicarboxylate (Table 2, entry b). Yield: 91%; ^1H NMR (200 MHz, $CDCl_3$): δ = 1.22–1.29 (dd, 12H), 4.9–5.05(m, 2H), 6.63 (d, 2H), 6.92 (br s, 1H), 7.16 (d, 2H), ^{13}C NMR (200 MHz, $CDCl_3$): δ = 22.06, 60.39, 115.56, 125.41, 126.22, 126.75, 127.6, 134.13, 155.18, 156.14; Anal. Calcd for $C_{14}H_{20}N_2O_5$: C, 56.75; H, 6.8; N, 9.45. Found: C, 56.71; H, 6.78; N, 9.42.
Diisopropyl 1-(4-hydroxy-2-methylphenyl)hydrazine-1,2-dicarboxylate (Table 2, entry c). Yield: 86%; ^1H NMR (200 MHz, $CDCl_3$): δ = 1.21–1.29 (dd, 12H), 2.03 (s, 3H), 4.89–5.04(m, 2H), 6.44 (d, 1H), 6.58 (d, 1H), 6.89 (br s, 1H), 7.06 (d, 1H). ^{13}C NMR (200 MHz, $CDCl_3$): δ = 22, 60.29, 69.96, 124.27, 133.12, 136.8, 155.88, 156.35, 157.4; Anal. Calcd for $C_{15}H_{22}N_2O_5$: C, 58.05; H, 7.15; N, 9.03. Found: C, 58.15; H, 7.14; N, 9.12.
Diisopropyl 1-(4-hydroxy-2,3-dimethylphenyl)hydrazine-1,2-dicarboxylate (Table 2, entry e). Yield: 79%; ^1H NMR (200 MHz, $CDCl_3$): δ = 1.16–1.28 (dd, 12H), 2.12 (s, 3H), 2.16 (s, 3H), 4.9–5.07(m, 2H), 6.85 (br s, 1H), 6.98 (m, 2H), ^{13}C NMR (200 MHz, $CDCl_3$): δ = 21.98, 32.1, 48.1, 60.41, 122.32, 127.11, 132.89, 151.71, 155.94, 156.32; Anal. Calcd for $C_{16}H_{24}N_2O_5$: C, 58.24; H, 7.46; N, 8.64. Found: C, 58.31; H, 7.5; N, 8.56.
Diisopropyl 1-(2,4,6-trimethylphenyl)hydrazine-1,2-dicarboxylate (Table 2, entry h). Yield: 73%; ^1H NMR (200 MHz, $CDCl_3$): δ = 1.4–1.58 (dd, 12H), 2.51 (s, 6H), 2.55 (s, 6H), 5.19–5.28 (m, 2H), 6.94 (br s, 1H), 7.13 (s, 1H), ^{13}C NMR (200 MHz, $CDCl_3$): δ = 18.19, 20.98, 21.92, 69.89, 129.18, 129.41, 135.91, 136.45, 137.84, 138.03, 155.49, 156.2; Anal. Calcd for $C_{18}H_{28}N_2O_4$: C, 64.26; H, 8.39; N, 8.33. Found: C, 64.29; H, 8.36; N, 8.34.
Diisopropyl 1-(3-chloro-4-hydroxyphenyl)hydrazine-1,2-dicarboxylate (Table 2, entry i). Yield: 83%; 1.13–1.28 (dd, 12H), 2.29 (s, 9H), 4.9–5.07(m, 2H), 6.71 (br s, 1H), 6.94 (s, 2H), ^{13}C NMR (200 MHz, $CDCl_3$): δ = 18.11, 20.91, 21.95, 70.54, 129.11, 129.33, 135.83, 136.05, 136.39, 137.77, 137.96, 155.6, 155.91; Anal. Calcd for $C_{17}H_{26}N_2O_4$: C, 63.33; H, 8.13; N, 8.69. Found: C, 63.31; H, 8.17; N, 8.72.
Diisopropyl 1-(4-fluorophenyl)hydrazine-1,2-dicarboxylate (Table 2, entry k). Yield: 43%; ^1H NMR (200 MHz, $CDCl_3$): δ = 1.56–1.66 (dd, 12H), 5.27 (m, 2H), 7.12 (d, 2H) 7.17 (br s, 1H), 7.58 (d, 2H), ^{13}C NMR (200 MHz, $CDCl_3$): δ = 22.7, 61.02, 116.19, 124.38, 126.85, 127.38, 127.84, 128.47, 134.76, 155.81, 156.78; Anal. Calcd for $C_{14}H_{19}FN_2O_4$: C, 56.37; H, 6.42; N, 9.39. Found: C, 56.36; H, 6.43; N, 9.41.