Chemistry of Heterocyclic Compounds, Vol. 46, No. 9, 2010

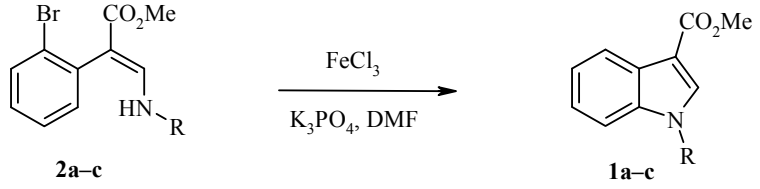
FERRIC CHLORIDE-CATALYZED SYNTHESIS OF INDOLES USING THE INTRAMOLECULAR AMINATION OF ARYL BROMIDES

F. S. Melkonyan[1], A. P. Topolyan[1], A. V. Karchava[1]*, and M. A. Yurovskaya[1]

Keywords: indole, ferric chloride, intramolecular N-arylation.

The great progress in the synthesis of heterocyclic compounds has been achieved due to the use of various transition metals as catalysts [1, 2]. Palladium catalysts are most often used among the transition metal catalysts for the synthesis of heterocyclic compounds [3-6]. However, despite the obvious advantages of such palladium catalysts, they also have a number of considerable disadvantages related to the high cost and toxicity of both palladium itself and the phosphine ligands often used in these reactions. The rapid recent development of methods using copper catalysts for various cross-coupling reactions can be attributed specifically to these disadvantages. Over the past decade, the "renewed" Ulmann reaction has become an important synthetic method for the creation of C–C and C-X bonds (X = N, O, S) [7]. However, iron catalysts are even more promising relative to cost and "green" chemistry. The feasibility of using such catalysts for cross-coupling reactions has recently been demonstrated [8-11]. The use of the bimetallic Fe/Cu catalyst system sometimes proves effective [12, 13]. Recently, Bonnamour and Bolm [14] have described the synthesis of 2-substituted benzoxazoles from the corresponding 2-haloacetanilides. The key step of this synthesis is intramolecular O-arylation using $FeCl_3$–2,2,6,6-tetramethylheptane-3,5-dione as the catalyst system. An additional example of a ferric chloride-catalyzed intramolecular O-arylation is the cyclization of methyl esters of 2-(2-bromophenyl)-3-oxopropionic acid, leading to the corresponding benzofurans [15].

In light of the advantages of using iron catalysts, we undertook a study of the feasibility of replacing copper catalysts in a synthetic strategy, which we previously employed for the preparation of N-substituted methyl esters of indole-3-carboxylic acids [16] and methyl esters of 1-aminoindole-3-carboxylic acids [17], with a catalyst containing ferric salts.



2a–c **1a–c**

a R = Bn, **b** R = *p*-$MeOC_6H_4$, **c** R = NMe_2

* To whom correspondence should be addressed, e-mail: karchava@org.chem.msu.ru.

[1]M. V. Lomonosov Moscow State University, Moscow 119991, Russia.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1429-1432, September, 2010. Original article submitted June 11, 2010.

We initially carried out the synthesis of indole **1a** from the corresponding enamine **2a** using the cyclization condition proposed in previous work [16], replacing CuI by $FeCl_3$. However, the yield of the reaction product was only 50% in this case (Table 1, experiment 1). Increasing the temperature to 110°C led to a more rapid conversion of enamine **2a** but the yield of cyclization product **1a** remained almost the same. Increasing the amount of K_3PO_4 to three equivalents gave indole **1a** in 77% yield (experiment 3). No significant increase in the yield of indole **1a** was observed using 25 mol % $FeCl_3$. Complete conversion of the starting reagent was noted after 30 h but this reaction led to a mixture of unidentified compounds (experiment 5). The use of the optimal conditions found for the cyclization of enamine **2a** (15 mol % $FeCl_3$, 3 equivalents K_3PO_4, DMF as solvent, reaction temperature 110°C) permitted a high yield of indole **1b**, which contains an aryl substituent at N-1. The time for complete conversion of enamine **2b** was 17 h (experiment 6). The use of a catalyst system containing 15 mol % $FeCl_3$ and two equivalents of K_3PO_4 in the synthesis of the methyl ester of 1-(dimethylamino)indole-3-carboxylic acid (**1c**) by cyclization of the corresponding enamine **2c** proved quite effective. When the reaction mixture in DMF was stirred at 75°C, complete conversion of starting enamine **2c** was observed after 15 h and the yield of indole **1c** was 60% (experiment 7). When the reaction temperature was raised to 110°C and the amount of K_3PO_4 used was increased to three equivalents, the time for complete conversion was reduced to 10 h but the yield of indole **2c** dropped to 50% (experiment 8). The use of 25 mol % $FeCl_3$ and two equivalents of K_3PO_4 proved optimal. In this case, the complete conversion of enamine **2c** was observed after 15 h upon stirring the reaction mixture in DMF at 85°C and the yield of indole **1c** was 77% (experiment 9).

Thus, we have shown that ferric chloride may be used as an efficient catalyst in intramolecular O-arylation reactions. We obtained methyl esters of indole-3-carboxylic acids containing alkyl (**1a**) and aryl substituents (**1b**) at the nitrogen atom as well as indole **1c** containing a dimethylamino group at N-1.

Methyl Ester of 1-Benzylindole-3-carboxylic Acid (1a). K_3PO_4 (0.636 g, 9 mmol) and $FeCl_3$ (73 mg, 0.45 mmol) were added to a solution of enamine **2a** [16] (1.038 g, 3 mmol) in DMF (3 ml). The rapidly stirred reaction mixture was heated to 110°C and maintained at this temperature until complete conversion of enamine **2a** was achieved as indicated by thin-layer chromatography. Then, the reaction mixture was cooled and the solvent was removed in vacuum. Water (10 ml) was added to the residue and the mixture was extracted with two 10-ml portions of ethyl acetate. The combined organic extracts were washed with two 15-ml portions of saturated aq. NaCl and dried over Na_2SO_4. The solvent was removed in vacuum. The residue was subjected to chromatography on a silica gel column (0.040-0.063 mm) using 20:1 hexane–ethyl acetate as the eluent to give 0.604 mg (76%) indole **1a** as pale-yellow crystals, mp 93-95°C (toluene–hexane). The parameters of the ^1H NMR, ^{13}C NMR, and mass spectra for the sample obtained of indole **1a** were identical to the data reported by Hwu et al. [18].

TABLE 1 Dependence of Yield of the Compounds **1a-c** on the Reaction Conditions

Experiment	Indole	$FeCl_3$, mol %	K_3PO_4, equiv.	T, °C	Time, h*	Yield, %
1	**1a**	15	2	75	27	50
2		15	2	110	15	55
3		15	3	110	15	77
4		25	3	110	15	78
5		0	3	110	30	0
6	**1b**	15	3	110	17	75
7	**1c**	15	2	75	15	60
8		15	3	110	10	50
9		25	2	85	15	77

* The reaction mixture was kept until complete conversion of compound **2** (control by TLC).

Methyl Ester of 1-(4-Methoxyphenyl)indole-3-carboxylic Acid (1b) was obtained analogously in 75% yield from enamine **2b** [16] as brown crystals; mp 123-125°C (toluene–hexane). The parameters of the ^{1}H NMR, ^{13}C NMR, and mass spectra for the sample obtained of indole **1b** were identical to the data reported by Belinna et al. [19].

Methyl Ester of 1-Dimethylaminoindole-3-carboxylic Acid (1c) was obtained analogously in 77% yield from enamine **2c** [17] as a brown oil. The parameters of the ^{1}H NMR, ^{13}C NMR, and mass spectra for the sample obtained of indole **1c** were identical to the data reported by Melkonyan et al. [17].

REFERENCES

1. I. Nakamura and Y. Yamamoto, *Chem. Rev.*, **104**, 2127 (2004).
2. N. Patil and Y. Yamamoto, *Chem. Rev.*, **108**, 3395 (2008).
3. J. P. Wolfe and J. S. Thomas, *Curr. Org. Chem.*, **9**, 625 (2005).
4. G. Kirsch, S. Hesse, and A. Comel, *Curr. Org. Syn.*, **1**, 47 (2004).
5. G. Zeni and R. C. Larock, *Chem. Rev.*, **106**, 4644 (2006).
6. B. Schlummer and U. Scholz, *Adv. Synth. Catal.*, **346**, 1599 (2004).
7. G. Evano, N. Blanchard, and M. Toumi, *Chem. Rev.*, **108**, 3054 (2008).
8. B. D. Sherry and A. Fürstner, *Acc. Chem. Res.*, **41**, 1500 (2008).
9. C. Bolm, J. Legros, J. Le Paih, and L. Zeni, *Chem. Rev.*, **104**, 6217 (2004).
10. A. Correa, O. Garsia Mancheno, and C. Bolm, *Chem. Soc. Rev.*, **37**, 1108 (2008).
11. K. Swapna, A. Vijar Kumar, V. Prakash Reddy, and K. Rama Rao, *J. Org. Chem.*, **74**, 7514 (2009).
12. C. M. Rao Volla and P. Vogel, *Tetrahedron Lett.*, **49**, 5961 (2008).
13. X. F. Wu and C. Darcel, *Eur. J. Org. Chem.*, 4753 (2009).
14. J. Bonnamour and C. Bolm, *Org. Lett.*, **10**, 2665 (2008).
15. F. Melkonyan, N. Golantsov, and A. Karchava, *Heterocycles*, **75**, 2973 (2008).
16. F. S. Melkonyan, A. V. Karchava, and M. A. Yurovskaya, *J. Org. Chem.*, **73**, 4275 (2008).
17. F. Melkonyan, A. Topolyan, M. Yurovskaya, and A. Karchava, *Eur. J. Org. Chem.*, 5952 (2008).
18. J. R. Hwu, H. V. Patel, R. J. Lin, and M. O. Gray, *J. Org. Chem.*, **59**, 1577 (1994).
19. F. Belinna, C. Calandri, S. Cauteruccio, and R. Rossi, *Eur. J. Org. Chem.*, 2147 (2007).