Pergamon

Tetrahedron Letters 42 (2001) 8111–8113

TETRAHEDRON LETTERS

Lithium perchlorate assisted one-pot three-component aminoalkylation of electron-rich aromatic compounds

Mohammad R. Saidi,* Najmoddin Azizi and M. Reza Naimi-Jamal

Department of Chemistry, Sharif University of Technology, PO Box 11345-9516, Tehran, Iran

Received 25 August 2001; accepted 14 September 2001

Abstract—A one-pot, three-component, Mannich reaction of electron-rich aromatic compounds with in situ prepared iminium salts in 5 M ethereal lithium perchlorate gives good yields of aminoalkylated products at room temperature.

The Mannich reaction has long been of great importance and a classical method for the aminoalkylation of aldehydes, and has been one of the most important basic reactions in organic chemistry for use in natural product and pharmaceutical chemistry.[1] The classical Mannich reaction has limited applications, and many attempts have been made to extend this reaction.[2] Direct aminoalkylation has great interest in synthetic organic chemistry and considerable importance for the synthesis of drugs, pesticides and natural products. Many methods of aminoalkylation of electron rich aromatic compounds have been studied to date. Katritzky and Risch have reported an improved aminoalkylation of β-naphthol and phenol derivatives with preformed iminium salts derived from aromatic aldehydes, in a two-step sequence with 26–92% yields.[3] Recently, we have reported the aminomethylation of electron-rich aromatic compounds under solvent-free conditions and the lithium perchlorate mediated, one-pot, three-component aminoalkylation of aldehydes for the preparation of a variety of amines and aminoesters, as well as functionalized alkylamines.[4]

The preparation and purification of iminium salts in a separate step, their hygroscopicity and susceptibility to hydrolysis (with the exception of Eschenmoser's salts),[5] led us to develop an alternative method for the aminoalkylation of electron-rich aromatic compounds. In continuation of our current work on the lithium perchlorate mediated aminoalkylation reaction,[6] we now wish to describe an efficient three-component and one-pot method for aminoalkylation of electron-rich aromatic compounds using aldehydes, (trimethylsilyl)dialkylamines, and an electron-rich aromatic compound such as α- or β-naphthol, indole, *N*-methylindole, coumarin or 6-hydroxyisoquinoline, at room temperature in a concentrated solution of lithium perchlorate in diethyl ether. The reaction of β-naphthol with in situ prepared iminium salts in a 5 M ethereal lithium perchlorate solution gives good yields of aminoalkylated aromatic and aliphatic compounds **1**–**11** with moderate (in the case of aliphatic aldehydes) to good yields. The yields appear to depend, not only on the nucleophilicity of the electron-rich aromatic compounds, but also on the reactivity of the iminium salt and the starting aldehyde. The results are summarized in Table 1. The aminoalkylation of 6-hydroxyisoquinoline with a preformed iminium salt is shown in Scheme 1.

Experimental

General. $LiClO_4$ (Fluka) was dried at 160°C and 10^{-1} Torr for 48 h. Ether was dried over Na/benzophenone under argon. IR spectra were taken on a Mattson 1000 Unicam FTIR, ^1H and ^{13}C NMR spectra were recorded on Bruker AC 80 instruments. All reactions were performed under argon. Chemicals were purchased from Fluka and used as received.

General procedure for the aminoalkylation of electron-rich aromatic compounds

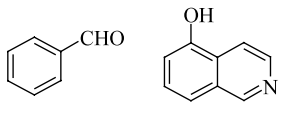
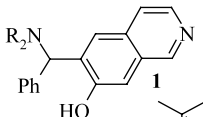
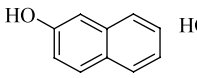
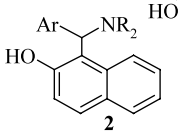
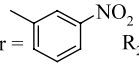
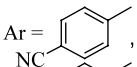
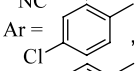
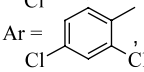
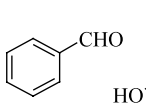
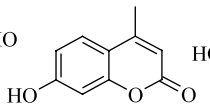
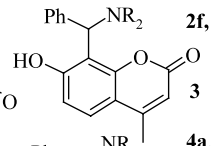
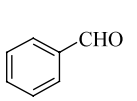
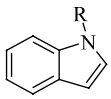
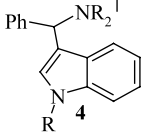
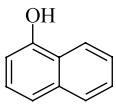
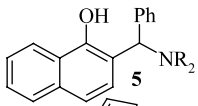
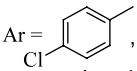
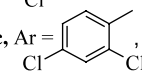
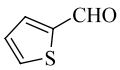
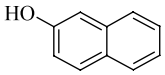
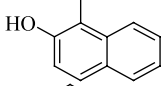
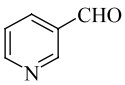
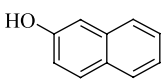
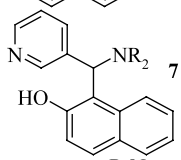
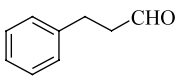
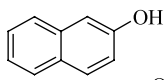
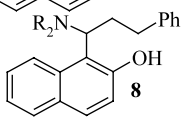
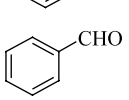
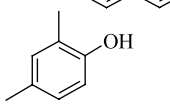
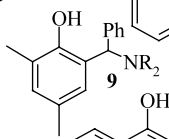
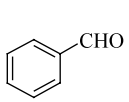
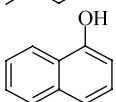
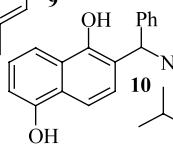
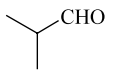
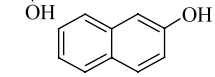
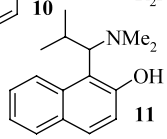
The aldehyde (2 mmol) and 3 mL of 5 M $LiClO_4$ in diethyl ether were placed in a 50 mL flask under argon

Keywords: aminoalkylation; Mannich reaction; lithium perchlorate; electron-rich aromatic compounds.

* Corresponding author. Fax: 0098 21 601 2983; e-mail: saidi@sharif.edu

0040-4039/01/$ - see front matter
PII: S0040-4039(01)01732-4

Table 1. $LiClO_4$-mediated aminoalkylation of electron-rich aromatic compounds

Starting aldehyde	Aromatic substrate	Product	%yield	Time, h
		 **1**	78	6.0
ArCHO		 **2**		
		2a, Ar = 	84	3.0
		2b, Ar = Ph, $R_2N = Me_2N$	70	1.0
		2c, Ar = Ph, R_2N = 	65	1.0
		2d, Ar = 	90	3.0
		2e, Ar = 	82	4.0
		2f, Ar = 	90	3.0
		 **3**	70	6.0
		4a, R = H, R_2N = 	84	6.0
		 **4**		
		4b, R = H, $R_2N = Me_2N$	70	6.0
		4c, R = CH_3, $R_2N = Me_2N$	65	6.0
		5a, Ar = Ph, R_2N = 	68	4.0
ArCHO		 **5**		
		5b, Ar = 	70	4.0
		5c, Ar = 	76	4.0
		 **6**	90	3.0
		 **7**	95	3.0
		 **8**	45	3.0
		 **9**	50	6.0
		 **10**	76	3.0
		 **11**	35	3.0

and stirred for 5 min. The (trimethylsilyl)dialkylamine (3 mmol) was added via a syringe. After 30 min, an electron-rich aromatic compound, such as β-naphthol (2 mmol), was added and the mixture was stirred at room temperature for a given time (Table 1), then water (20 mL) and dichloromethane (20 mL) were added. The organic phase was separated, dried over $MgSO_4$, and the solvent was removed using a rotary evaporator. The crude product was further purified by column chromatography on basic alumina and was

Scheme 1.

characterized by comparison of IR and NMR (^{1}H and ^{13}C) spectra with those of an authentic sample. Yields refer to pure isolated products.

Caution: Although we did not have an accident using lithium perchlorate ($LiClO_4$), it is advisable to dry lithium perchlorate in a hood behind a lab-shield.

In conclusion, a mild, one-pot and fast, aminoalkylation of β-naphthol, 2,4-dimethyl-phenol, 6-hydroxyisoquinoline or 7-hydroxycoumarin with in situ prepared iminium salts at rt has been achieved in good to moderate yields. The reaction time was 1–6 h.

Acknowledgements

We thank 'Volkswagen-Stiftung, Federal Republic of Germany' for financial support towards the purchase of chemicals and equipment. M.R.S. thanks the Ministry of Science, Research and Technology of Iran for partial financial support.

References

1. (a) Paqett, L. O., Ed. *Encyclopedia of Reagents for Organic Synthesis*; Wiley: UK, 1995; Vol. 4, p. 2582; (b) Tramontini, M.; Angiolini, L. *Tetrahedron* **1990**, *46*, 1791–1837.
2. (a) Heaney, H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, p. 953; (b) Loh, T.-P.; Wei, L.-L. *Tetrahedron Lett*. **1998**, *39*, 323–326; (c) Katritzky, A. R.; Fan, W.-Q.; Long, Q.-H. *Synthesis* **1993**, 229–232.
3. (a) Grumbach, H.-J.; Arend, M.; Risch, N. *Synthesis* **1996**, 883–887; (b) Katritzky, A. R.; Abdel-Fattah, A. A. A.; Tymoshenko, D. O.; Belyakov, S. A.; Ghiviriga, I.; Steel, P. J. *J. Org. Chem*. **1999**, *64*, 6071–6075; (c) Sharifi, A.; Mirzaei, M.; Naimi-Jamal, M. R. *Monatsh. Chem*. **2001**, *132*, 875–880.
4. (a) Saidi, M. R.; Hydari, A.; Ipaktschi, J. *Chem. Ber*. **1994**, *127*, 1761–1764; (b) Saidi, M. R.; Khalaji, H. R.; Ipaktschi, J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1983–1986; (c) Saidi, M. R.; Khalaji, H. R. *J. Chem. Res. (S)* **1997**, 340–341; (d) Mojtahedi, M. M.; Sharifi, A.; Mohsenzadeh, F.; Saidi, M. R. *Synth. Commun*. **2000**, *30*, 69–72.
5. Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed. Engl*. **1998**, *37*, 1044–1070.
6. (a) Naimi-Jamal, M. R.; Mojtahedi, M. M.; Ipaktschi, J.; Saidi, M. R. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3709–3711; (b) Naimi-Jamal, M. R.; Ipaktschi, J.; Saidi, M. R. *Eur. J. Org. Chem*. **2000**, 1735–1739; (c) Saidi, M. R.; Azizi, N.; Zali-Boinee, H. *Tetrahedron* **2001**, *57*, 6829–6832.