Pergamon

Tetrahedron Letters, Vol. 37, No. 47, pp. 8487-8488, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01971-5

Synthesis of Arylpiperazines *via* Nucleophilic Aromatic Substitution of (η^6-Fluoroarene)tricarbonylchromium Complexes

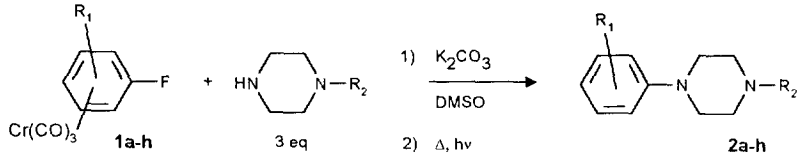
Michel Perez,* Pierre Potier and Serge Halazy

Division de Chimie Médicinale IV, Centre de Recherche Pierre Fabre
17 ave. Jean Moulin, 81106 Castres Cédex France

Abstract: A one-pot, high yield preparation procedure for the synthesis of arylpiperazines using a nucleophilic aromatic substitution of (η^6-fluoroarene)tricarbonylchromium complexes (including those bearing electron donating groups) is described. A new, easy and fast decomplexation procedure, in DMSO as solvent, is also presented. Copyright © 1996 Elsevier Science Ltd

The introduction of a piperazine moiety into aromatic compounds is of particular importance in the field of medicinal chemistry. Very recently, several new methods have been proposed for the synthesis of such compounds using solid support[1] or palladium-catalyzed aromatic amination reactions.[2]

It is well established that tricarbonylchromium complexes of arylhalides undergo nucleophilic replacement of halogen much more rapidly than does the parent halobenzene.[3] As part of our research program concerning 5-HT_{1D} receptor agonists,[4] we needed to develop a more efficient and general synthetic access to arylpiperazines. We report here a protocol for the use of (η^6-fluoroarene)tricarbonylchromium complexes for the synthesis of arylpiperazines (Scheme 1).



Scheme 1

We first investigated the reaction of (η^6-fluorobenzene)tricarbonylchromium complex[5] with several piperazines in acetonitrile[3] as solvent and with K_2CO_3 as a base (entries a-c, table I). This two steps procedure afforded the desired compounds (**2a-c**) in high yields but in very long reaction times. To optimize the reaction conditions, we decided to use DMSO since this solvent is often employed in S_NAr reactions.[6] We also decided to limit the excess of piperazine and K_2CO_3. Finally, to shorten the overall reaction time we tried the decomplexation reaction at higher temperature, in the same flask, without isolation of the intermediate complex. Under these conditions, the reaction proceeds much more rapidly and more efficiently (compare entries c and d) and the corresponding phenylpiperazines were obtained in very good overall yields. Thus, this result demonstrates the particular interest of DMSO as solvent for both reaction steps.

We also investigated the reaction of (η^6-fluoroanisole)tricarbonylchromium complexes[5] (**1e-h**) with piperazine derivatives since electron-donating groups are often a limitation in S_NAr reactions.

Following the same procedure, the corresponding methoxyphenylpiperazine derivatives were obtained in high yields (95 to 100 %). Very interestingly, when piperazine itself was employed as nucleophile (entries a, e, g, h) the formation of symmetrical N,N'-bisarylpiperazine derivatives was never observed, thus allowing the direct preparation of unprotected compounds.

Table I: Preparation of arylpiperazines from (η^6-fluoroarene)tricarbonylchromium complexes.

					S_NAr reaction			decomplexation reaction			
Entry	**R_1**	**R_2**	**eq**	**Solvent**	**K_2CO_3 eq**	**Time**	**Yield %**	**T °C**	**Time**	**Yield %**	**mp °C**
a	H	H	8	CH_3CN	2	2 days	88	25	3 days	96	oil
b	H	CH_3	8	CH_3CN	2	20 h	95	25	3 days	96	oil
c	H	BOC	8	CH_3CN	2	2 days	85	-	-	-	-
d	H	BOC	3	DMSO	1.2	2.5 h	-[a]	80	4.5 h	98[b]	68
e	4-OMe	H	3	DMSO	1.2	3.5 h	-[a]	80	4 h	95[b]	oil
f	4-OMe	BOC	3	DMSO	1.2	47 h	-[a]	80	4 h	62[b]	87
g	3-OMe	H	3	DMSO	1.2	0.7 h	-[a]	80	3 h	100[b]	oil
h	2-OMe	H	3	DMSO	1.2	3 h	-[a]	80	3.5 h	96[b]	oil

[a] not isolated; [b] isolated yield for both steps

In summary, the method presented here offers a useful one-pot procedure for the preparation of protected or unprotected arylpiperazine derivatives from (η^6-fluoroarene)tricarbonylchromium complexes. The method has been successfully applied to electron rich systems and a rapid, *in situ* decomplexation procedure has been developed using DMSO as solvent.

Acknowledgement: We thank Drs J-P. Gotteland and C. Jorand-Lebrun for helpful discussions and Ms E. Dupeyron for secretarial assistance.

Typical experimental procedure:

Synthesis of **2d**: A mixture of **1d** (200 mg, 0.86 mmol), N-BOC-piperazine (481 mg, 2.58 mmol) and K_2CO_3 (143 mg, 1.03 mmol) in DMSO (2 mL) was stirred at 25 °C under argon and in the dark (aluminium foil), for 2.5 h. After that time, light protection and argon inlet were removed and the mixture was heated at 80 °C for 4.5 h. The green mixture obtained was diluted with EtOAc, washed with water, dried (Na_2SO_4) and concentrated. The crude product was chromatographed (hexane/acetone, 18/1) to give 221 mg (98%) of a white powder. mp 68 °C, ^{1}H NMR (DMSO-d6) δ (ppm) 1.43 (s, 9H, tBu), 3.09 (t, 4H, J = 5.5 Hz, CH_2), 3.47 (t, 4H, J = 7.5 Hz, CH_2), 6.82 (t, 1H, J = 7.5 Hz, Ar), 6.96 (d, 2H, J = 8.0 Hz, Ar), 7.24 (dd, 2H, J = 7.5 and 8 Hz, Ar).

References

1. Mishani, E.; Dence, C.S.; McCarthy, F.J.; Welch, M.J. *Tetrahedron Lett.*, **1996**, *37*, 319-322.
2. Zhao, S.-H.; Miller, A.K.; Berger, J.; Flippin, L.A. *Tetrahedron Lett.*, **1996**, *37*, 4463-4466.
3. (a) Nicholls, B.; Whiting, M.C. *J. Chem. Soc.*, **1959**, 551; (b) Bunnett, J.F.; Hermann, H. *J.Org. Chem.*, **1971**, *36*, 4081-4088.
4. Perez, M.; Fourrier, C.;Sigogneau, I.; Pauwels, P.J.; Palmier, C.; John, G.W.; Valentin, J.P.; and Halazy, S. *J.Med.Chem.*, **1995**, *38*, 3602-3607.
5. Mahaffy, C.A.L.; Pauson, P.L. *Inorg. Synth.*, **1979**, *19*, 154-158.
6. Bader, H.; Hansen, A.R.; McCarty, F.J. *J. Org. Chem.*, **1966**, *31*, 2319-2321.

(*Received in France* 9 *September* 1996; *accepted* 2 *October* 1996)