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Effective Monoallylation of Anilines Catalyzed by Supported KF

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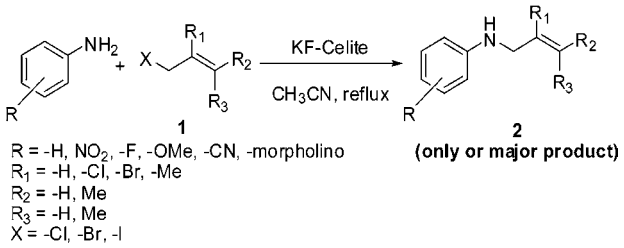
ABSTRACT



A mild and straightforward monoallylation procedure for different anilines is described using the efficient, inexpensive, noncorrosive, and environmentally friendly reagent KF-Celite. By using only a 1/1.2 stoichiometric ratio of electrophilic reagent to aniline, in very short reaction times, the monoallylated products are obtained in high isolated yields via this procedure, which works very effectively regardless of the electronic nature of the substituent on the ring, although electron withdrawing groups make the reactions go even faster.

Allylic secondary amines are useful building blocks in organic chemistry,[1] making improved procedures for their synthesis or new preparative routes an attractive research field.

In this sense, the transition-metal catalyzed allylation of anilines with allylic alcohols constitutes an interesting procedure for the synthesis of *N*-allylanilines. In this regard, significant progress has been made using transition-metal catalysts prepared from palladium[2] or titanium.[3] On the other hand, the synthesis of aromatic secondary amines through classical methodologies[4] is generally complicated by the formation of significant amounts of *N*-dialkylation products, which lowers the chemoselectivity and the economy of the process.[5] To overcome this problem, the use of inorganic catalysts such as zeolites[6] has been reported as a methodology that provides selectively *N*-allylaniline derivatives, even when deactivating groups are present in the aromatic moiety. Nevertheless, an excess of amine (to prevent overallylation) and extended reaction times are demanded, because of the low nucleophilicity of the aniline nitrogen.

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(2) (a) Ozawa, F.; Okamoto, H.; Kawagishi, S.; Yamamoto, S.; Minami, T.; Yoshifuji, M. *J. Am. Chem. Soc.* **2002**, *124*, 10968. (b) Yang, S.-C.; Tsai, Y.-C. *Organometallics* **2001**, *20*, 763. (c) Hsu, Y.-C.; Gan, K.-H.; Yang, S.-C. *Chem. Pharm. Bull.* **2005**, *53*, 1266. (d) Yang, S.-C.; Hsu, Y.-C.; Gan, K.-H. *Tetrahedron* **2006**, *62*, 3949. (e) Johns, A. M.; Utsunomiya, M.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 1828. (f) Tsuji, J. *Organic Synthesis with Palladium Compounds*; Springer: Heidelberg, Germany, 1980. (g) Yang, S.-C.; Hung, C.-W. *J. Org. Chem.* **1999**, *64*, 5000. (h) Moreno-Mañas, M.; Morral, L.; Pleixats, R. *J. Org. Chem.* **1998**, *63*, 6160.

(3) Ramanathan, B.; Odom, A. L. *J. Am. Chem. Soc.* **2006**, *128*, 9344.

(4) For a review, see: Salvatore, R. N.; Yoon, C. H.; Jung, K. W. *Tetrahedron* **2001**, *57*, 7785 and references therein.

(5) (a) Fellows, I. M.; Kaelin, D. E.; Martin, S. F. *J. Am. Chem. Soc.* **2000**, *122*, 10781. (b) D'Amico, J. J.; Harman, M. W.; Cooper, R. H. *J. Am. Chem. Soc.* **1957**, *79*, 5270. (c) Mori, M.; Chiba, K.; Okita, M.; Kayo, I.; Ban, Y. *Tetrahedron* **1985**, *41*, 375. (d) Pollard, C. B.; Parcell, R. F. *J. Am. Chem. Soc.* **1951**, *73*, 2925. (e) Barluenga, J.; Canteli, R. M.; Flórez, J. *J. Org. Chem.* **1996**, *61*, 3753. (f) Capella, L.; Montevecchi, P. C.; Navacchia, M. L. *J. Org. Chem.* **1995**, *60*, 7424. (g) Barluenga, J.; Foubelo, F.; Fañanás, F. J.; Yus, M. *J. Chem. Soc., Perkin Trans. 1* **1989**, 553. (h) Oh, H. K.; Koh, H. J.; Lee, I. *J. Chem. Soc., Perkin Trans. 2* **1991**, 1981. (i) Oh, H. K.; Shin, C. H.; Lee, I. *J. Phys. Org. Chem.* **1992**, *5*, 731. (j) Lee, I.; Kang, H. K.; Lee, H. W. *J. Am. Chem. Soc.* **1987**, *109*, 7472. (k) Oh, H. K.; Jeong, E.-M.; Lee, I. *Bull. Korean Chem. Soc.* **1998**, *19*, 1334. (l) Nazarov, S. I.; Magerramov, M. N. *Russ. J. Org. Chem.* **1997**, *33*, 66. (m) McCall, I.; Proctor, G. R.; Purdie, L. *J. Chem. Soc. C* **1970**, 1126

(6) Onaka, M.; Umezono, A.; Kawai, M.; Izumi, Y. *J. Chem. Soc., Chem. Commun.* **1985**, 1202.

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Alkaline fluorides have shown their efficacy for alkylating both aliphatic and aromatic amines. The capability of a fluoride anion to catalyze *N*-alkylation has been related, as shown in Figure 1, to its ability to form a hydrogen bond

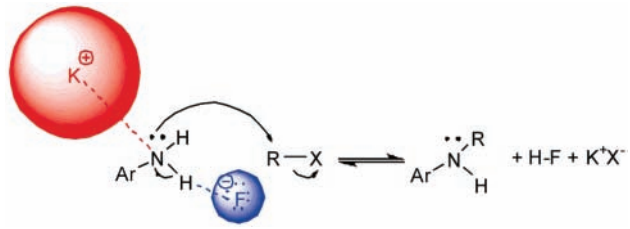
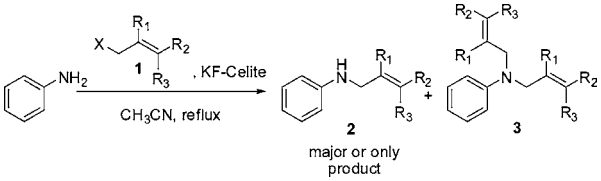


Figure 1. Mechanism of KF-catalyzed N-alkylation

with the amine proton, therefore enhancing the Lewis acid behavior of the metal.[7,8]

In this paper, an efficient improvement of the selective *N*-allylation of anilines using KF-Celite in acetonitrile at reflux is described. The design of the synthesis is represented in Scheme 1. In a typical experiment,[9] the electrophilic

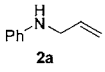
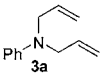
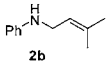
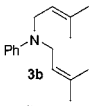
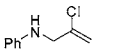
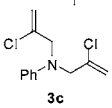
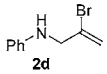
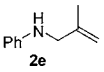
Scheme 1. Synthesis of *N*-Allyl Anilines



reagent (1.00 mmol) is added to a suspension of the catalyst (1.25 mmol) and a small excess of aniline (1.20 mmol) in acetonitrile. The results obtained, showing the isolated yields of the corresponding compounds, are shown in Table 1.

As can be seen, even though a small excess of aromatic amine was used, the corresponding *N*-allylaniline was always recovered as the predominant or exclusive product. In fact, *N*,*N*-diallylaniline production decreased as the molecular size (H < Cl < Br < CH_3, entries 1, 3, 4, and 5) of the terminal vinyl substituent increased and nucleophilic displacement on 2,3-dibromopropene (**1d**) or on 3-chloro-2-methylpropene (**1e**) did not afford any of the tertiary aniline products.

Table 1. N-Allylation of Aniline Using Different Allyl Halides

entry	allylating agent	time (h)	(allyl)NHPh	%[a]	(allyl)$_2$NPh	%[a]
1	 **1a**	2	 **2a**	82	 **3a**	13
2	 **1b**	4.5	 **2b**	83	 **3b**	10
3	 **1c**	6	 **2c**	86	 **3c**	8
4	 **1d**	7	 **2d**	92	----------	
5[b]	 **1e**	7	 **2e**	87	----------	

[a] Isolated yields. [b] Temperature = 70 °C.

Unhindered allyl halides such as allyl iodide (**1a**), 1-bromo-3-methylbut-2-ene (**1b**), and 3-iodo-2-chloropropene (**1c**) led to similar or higher chemoselectivities compared to previously reported methods.[2a,d] More concretely, we have improved the stoichiometric ratio between electrophilic reagent and aniline under our mild reaction conditions. In fact, we use a 1.2/1 ratio, compared to the previously reported ratios (4/1) to obtain similar yields in alkylation with KF-Celite.[7a] Furthermore, Ramanathan and Odom,[3] who use allylic alcohols, reported only a 51% of isolated yield of **2a** employing a 3/1 ratio of aniline versus allylic alcohol.

The results presented in Table 1 show how the allylation of aniline was obtained with excellent efficiency using different allyl halides, which gave rise to good isolated yields of the corresponding *N*-monoallyl anilines. When using halides containing electron-withdrawing groups (entries 3 and 4) the reaction rates were somewhat slower. These differences in reactivity could be related to deactivation of the allyl moiety promoted by the substituent.[6k] However, as indicated by the results in entry 4, the electronic properties of these functionalities do not affect reaction yields. Furthermore, no traces of any secondary product were detected by using this methodology, as shown by the results obtained when **1b** was employed as allylating agent (entry 2), compared to the undesired allylic rearrangement described in the synthesis of **2b** using allylic alcohols.[2d]

A more detailed study of the influence of the temperature on the kinetics of the *N*-allylation (shown in Table 2) has indicated that, at the acetonitrile reflux temperature (82 °C), aniline undergoes *N*-allylation very smoothly to afford the best results in terms of both reaction time and chemoselectivity.

It must be pointed that the products could also be obtained in good yield when the reaction was run at 35 °C (entry 6) or at 60 °C (entry 7); as can be seen, at 82 °C, the KF-

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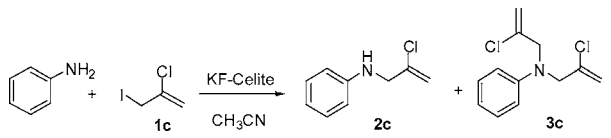
(9) Typical experimental procedure: To a stirred solution of aniline derivative (1.20 mmol) and KF-Celite (1.25 mmol) in anhydrous acetonitrile (3.5 mL), the allyl halide (1.00 mmol) was added. Then, the mixture was continued for stirring at reflux up to completion of the reaction. The reaction mixture was filtered to remove catalyst and rinsed several times with dichloromethane, after the filtrate was evaporated under reduced pression. The product was purified, whenever necessary, by column chromatography on silica gel using various solvent systems as eluents.

Table 2. Effect of Temperature on Allylation of Aniline Using **1c**

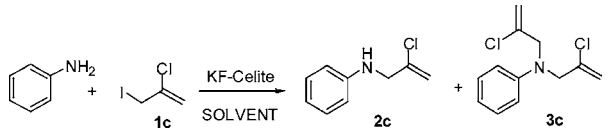


entry	temp °C	time h	yield of **2c** %	yield of **3c** %	ratio **2c/3c**
6	35	24	52	20	2.6
7	60	14	68	18	3.4
8	82	5	83	8	10.4

Celite catalysis gives its highest synthetic performance. Thus, the regioselectivity of the process is temperature dependent.

To study the influence of the solvent, Table 3 shows the results obtained with polar aprotic solvents such as DMF,

Table 3. Solvent Effect on KF-Celite Catalyzed Allylation of Aniline with **1c**



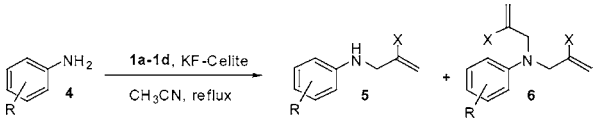
entry	solvent	time h	temp °C	yield of **2c** %	yield of **3c** %	ratio **2c/3c**
9	DMF	18	82	70	13	5.4
10	DMSO	18	82	60	18	3.3
11	THF	24	66	68	14	4.8
12	Me_2CO	24	55	70	19	3.7

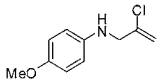
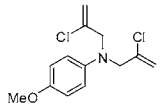
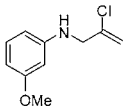
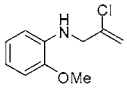
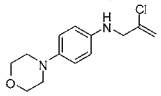
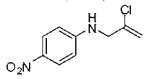
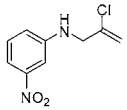
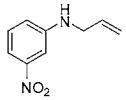
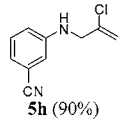
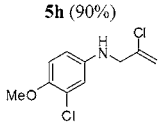
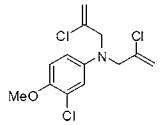
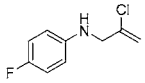
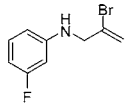
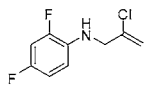
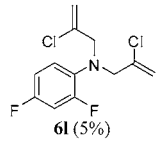
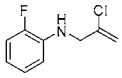
DMSO, THF, and acetone. Clearly, the solvent does not alter the chemoselectivity, but the reaction was more sluggish in these solvents when compared with acetonitrile (entry 8).

We also studied the influence of different substituents in the aromatic moiety to study the applicability of this methodology. The obtained products (some of them described for the first time) are shown in Table 4.

Allylation of anilines substituted with both electron-donating (entries 13 to 16) and electron-withdrawing groups (EWGs) (entries 17 to 20) gives excellent yields of the corresponding *N*-monoallylanilines as the predominant or exclusive reaction products with 2-chloro-3-iodopropene **1c**, in really short reaction times, ranging from 2.5 h (entries 18 and 20) to 4 h (entry 17). When electron-withdrawing groups are introduced (entries 17−20 and 22−25), the best results in terms of chemoselectivity, yield, and reaction times are obtained. The observed differences in reactivity promoted by the different electronic nature of the substituents could be related to the acidity of the corresponding anilines: thus, among nitroanilines, *m*-nitro (entries 18−19) led to higher yields of the isolated monoallyl anilines (sole reaction products) compared to the para regioisomer (entry 17), maybe

Table 4. N-allylation of Substituted Anilines (**4a**−**c**)



run	reagent/ time (h)	R-	(allyl)NPh (%)	$(allyl)_2NPh$ (%)
13	**1c**/6	4-MeO-		
		4a	**5a** (79%)	**6a** (10%)
14	**1c**/8	3-MeO-		Not detected
		4b	**5b** (67%)	
15	**1c**/7	2-MeO-		Not detected
		4c	**5c** (75%)	
16	**1c**/5	4-morpholino		Not detected
		4d	**5d** (83%)	
17	**1c**/4	4-NO_2		Not detected
		4e	**5e** (87%)	
18	**1c**/2.5	3-NO_2		Not detected
		4f	**5f** (93%)	
19	**1a**/3	3-NO_2		Not detected
		4g	**5g** (90%)	
20	**1c**/2.5	3-CN		Not detected
		4h	**5h** (90%)	
21	**1c**/6	3-chloro-4-mehoxy		
		4i	**5i** (69%)	**6i** (7%)
22	**1c**/ 5	4-fluoro		Not detected
		4j	**5j** (80%)	
23	**1d**/ 3.5	3-fluoro		Not detected
		4k	**5k** (85%)	
24	**1c**/ 7	2,4-difluoro		
		4l	**5l** (78%)	**6l** (5%)
25	**1c**/ 36	2-fluoro		Not detected
			5m (79%)	

because of the higher basicity of the meta isomer.[10] Under similar experimental conditions the more acidic ortho isomer did not react after 48 h. Perhaps this is due to both intramolecular hydrogen-bond formation[11] (which would obstruct the proton removal by the fluoride) and steric hindrance. A similar pattern was observed with fluoroanilines (entries 22−24), where, once again, the best yields were obtained for the meta isomer. Unlike *o*-nitro aniline (no reaction at all after 48 h), *o*-fluoroaniline was N-allylated, (entry 25); although the reaction was considerably slower (36 h), probably because the fluoro substituent does not introduce such a significant steric hindrance into the molecule unlike the nitro. However, intramolecular NH−H···F hydrogen bonding in the ortho position is much weaker[12] than the corresponding NH−H···O_2N so that the depressing effect of the *o*-fluoro group on the overall reaction rate is smaller compared to the *o*-nitro. Similarly, the reaction with *m*-aminobenzonitrile (entry 20) was also very straightforward. In any case, compared to reported data on the alkylation of deactivated anilines,[4] our methodology leads to much better yields and selectivity in the monoalkylation process. In fact, allylation of deactivated anilines to secondary amines has only been reported in an alumina or zeolite-catalyzed process by Onaka et al.[5] and in some specific regioisomer of nitroaniline by Hsu et al.[2c]

On the other hand, the effect of an electron-donating group (EDG) such as methoxy (entries 13−15) was predictable on the basis of position/nucleophility correlation; thus, *p*-methoxy, the most nucleophilic, reacted in the shortest time (entry 1), followed by the *o*-methoxy regioisomer (run 3), and finally by the *m*-methoxy (run 3). The mesomeric effect improves the reaction rate of the allylation of anilines bearing a *p*-substituted electron donating group; this fact was observed also in the morpholinoaniline (entry 16). Among all *m*-substituted anilines, 3-chloro-4-methoxy was the only one (entry 21) that afforded a small amount of diallylated product.

Comparing various 2-substituted anilines, the steric effect of the substituent, as well as its electronic nature, plays an important role in the success of *N*-allylation via our method. 2-Methoxy and 2,4-difluoro (runs 15 and 24) were the only reactive anilines with a substituent in the hindered ortho position that reacted, while a substituent with more steric hindrance such as 2-nitro did not react under the described experimental conditions.

To conclude, the synthetic protocol described herein allows the synthesis of almost exclusively secondary allylic anilines in short reaction times, improving the stoichiometric relation between amine and allylating agent. Therefore, we encourage the use of KF-Celite as an efficient, inexpensive, noncorrosive, and environmentally friendly reagent for the synthesis of allylic anilines.

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Supporting Information Available: General experimental procedures, full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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