Desulfonylation of *N*-Sulfonyl Tetrahydroisoquinoline Derivatives by Potassium Fluoride on Alumina Under Microwave Irradiation: Selective Synthesis of 3,4-Dihydroisoquinolines and Isoquinolines

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Abstract: In a solvent-free system, the microwave irradiation of mixtures of *N*-sulfonyl tetrahydroisoquinolines and 37% potassium fluoride supported on alumina selectively furnished 3,4-dihydroisoquinolines or isoquinolines, depending upon the reaction time.

Key words: isoquinolines, 3,4-dihydroisoquinolines, KF on alumina, microwave-assisted desulfonylation

Chemical transformations carried out with supported reagents under dry conditions have several significant advantages over reactions traditionally run in solution; they offer easier separation of the products, new or better selectivities, faster processes or milder reaction conditions, less waste problems and the possibility of working in a continuous way.[1]

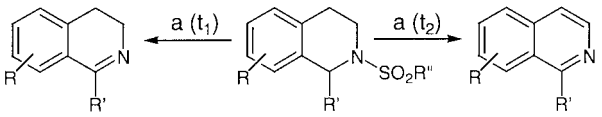
Potassium fluoride on alumina (KF/Al_2O_3) has been reported as a solid supported reagent for alkylation,[2] elimination,[3] addition,[4] condensation,[5] enolization, desilylation,[6] coupling[7] and other useful reactions. It has been shown that during the impregnation-activation procedure, the salt reacts with aluminium oxide forming K_3AlF_6 and an active mixture of KOH and potassium aluminate on the surface of the solid support,[8] which would contribute to explain its reactivity.

On the other hand, the enhancement of chemical transformations by microwave irradiation of organic molecules supported on inorganic solids has experienced an enormous growth in recent years,[9] as this technique is manipulatively simple, can be conducted rapidly and provides products in high yields employing solvent-free conditions.

Recent work informed that under microwave assistance KF/Al_2O_3 cleaves sulfonamides to the corresponding amines in dry conditions.[10] However, the irradiation of mixtures of *N*-sulfonyl isoquinoline derivatives and KF/Al_2O_3 has not been studied to date.

N-sulfonyl-type protecting groups are widely used in isoquinoline chemistry, specially in the *N*-activated Pictet–Spengler synthesis[11,12] and in many variations of the Pomerantz–Fritsch sequence.[13] Removal of the sulfonyl moiety by taking advantage of the different oxidation states of sulfur has been employed to broaden the scope of these synthetic protocols, but only a few methods have been described.[11,13]

Herein, we wish to report the selective elaboration of 3,4-dihydroisoquinolines and isoquinolines (Scheme 1) by the microwave-assisted oxidative desulfonylation and subsequent dehydrogenation (for isoquinolines) of *N*-sulfonyl tetrahydroisoquinolines with KF/Al_2O_3 as solid supported reagent, in non-solvent conditions.



Scheme 1 Reagents and Conditions: a) 37% KF/Al_2O_3, Microwaves (time: $t_1 < t_2$).

Starting tetrahydroisoquinolines consigned in Table 1 were prepared employing a modified activated Pictet–Spengler procedure, by reaction of α-phenylchalcogen-α-halocarbonyls as aldehyde surrogates with conveniently substituted *N*-tosyl-β-phenethylamines, under Lewis acids promotion.[11b,12]

As shown in Table 1, submission of the *N*-sulfonyl heterocycles to microwave irradiation (490 Watts) provided good yields of the corresponding 3,4-dihydroisoquinolines upon a short reaction period (10–20 s), uncontaminated with the related isoquinolines; interestingly, however, increasing the irradiation time completely transformed the starting materials into the corresponding isoquinolines, providing a highly selective and convenient strategy to access both classes of compounds. In spite that hydrolytic cleavage of the *N*-*S* bond with formation of the desulfonylated tetrahydroisoquinolines[10] could not be completely ruled out, such compounds could neither be detected or isolated.

In order to assure that these results were not due to a purely thermal effect, conventional heating experiments were performed. It has been reported that the temperature of an

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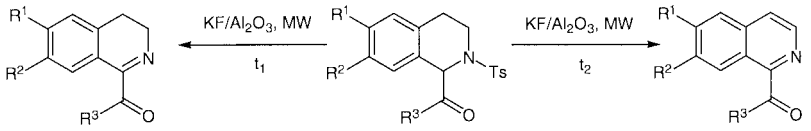
Table 1 Synthesis of 3,4-Dihydroisoquinolines and Isoquinolines by Microwave-Assisted Reaction of *N*-Sulfonyl Tetrahydroisoquinoline Derivatives with KF Supported on Alumina[22]



Entry	R^1	R^2	R^3	Dihydroisoquinolines		Isoquinolines	
				Time (t_1, s)[a]	Yield (%)[b]	Time (t_2, s)[a]	Yield (%)[b]
1[c]	H	H	C_6H_5	10	60	20	56
2	H	H	*t*Bu	15	71	30	73
3	-OCH_2O-		C_6H_5	10	87	30	86
4[d]	-OCH_2O-		3-MeO-C_6H_4	20	92	60	69
5[e]	-OCH_2O-		4-MeO-C_6H_4	–	–	120	49
6[f]	MeO	MeO	4-MeO-C_6H_4	10	77	–	–

[a] Irradiation time at 490 W in a domestic microwave oven.
[b] Isolated yield after column chromatography.
[c] The resulting isoquinoline has been previously synthesized.[14]
[d] Conventional heating of the *N*-sulfonyl tetrahydroisoquinoline with KF/Al_2O_3 in toluene afforded the related 3,4-dihydroisoquinoline after a 48 h reflux period.
[e] The resulting isoquinoline is a natural product isolated from *Oocotea pulcella*, mp 152–154 ºC (Lit.[15] 152–153 ºC).
[f] The resulting 3,4-dihydroisoquinoline is *O*,*O*-dimethyl longifolonine, mp 91–92 ºC; IR and ^1H NMR spectra are in agreement with those reported in the literature.[16b]

alumina bath (heat sink) inside a Sears Kenmore microwave oven equipped with a turntable at full power (900 W) was found to be ≈ 65 ºC after 30 s of irradiation;[17] therefore, the tetrahydroisoquinoline depicted in entry 4 of Table 1 was mixed with KF/Al_2O_3 and aliquots of the resulting powder were heated at 90 ºC in an oil bath or heated under reflux in toluene. In the first case, no reaction was observed after heating for 24 h; in the experiment employing toluene as solvent, however, it was noticed that at the same time the reaction consisted of a 2:1 mixture of the 3,4-dihydroisoquinoline and the starting tetrahydroisoquinoline. Complete consumption of the starting material was achieved in 48 h, but no 1-benzoylisoquinoline could be detected, 3,4-dihydroisoquinoline being the the only reaction product. In addition, no reaction was observed when the tetrahydroisoquinoline was submitted to microwave irradiation in the absence of KF/Al_2O_3.

Many 1-benzoylisoquinolines and 1-benzoyl-3,4-dihydroisoquinolines have been isolated from different plants. Noteworthy, this strategy provides new alternatives for the syntheses of these type of natural products and their derivatives, as illustrated by the convenient elaboration of the unnamed base isolated from *Oocotea pulcella*,[15] depicted in entry 5 and of *O*,*O*-dimethyl longifolonine,[16] obtained as shown in entry 6.

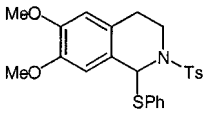
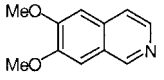
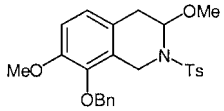
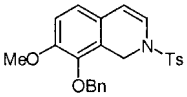
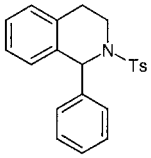
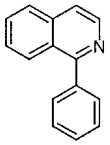
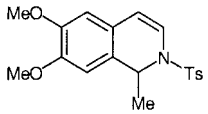
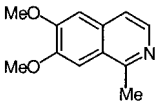
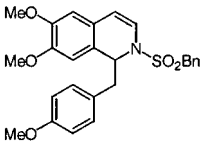
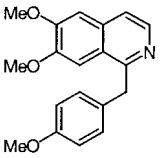
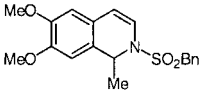
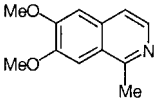
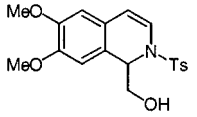
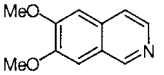
In order to explore more in depth the scope of the above transformations, a series of *N*-sulfonyl-1,2-dihydroisoquinolines and *N*-sulfonyl-1,2,3,4-tetrahydroisoquinolines was synthesized[18] following Jackson's protocol[13] and submitted to microwave irradiation, with the results consigned in Table 2.

In the cases of *N*-sulfonyl *N*,*S*- and *N*,*O*- acetals (entries 1 and 2), it was observed that while the thio compound furnished an isoquinoline with concomitant loss of the 1-thiophenyl moiety, the 3-methoxy tetrahydroisoquinoline quickly lost methanol, giving the related *N*-sulfonyl-1,2-dihydroisoquinoline in good yield, but no isoquinoline was produced, even under prolonged microwave heating, which caused complete product decomposition. The 1-phenyl tetrahydroisoquinoline of entry 3, however, furnished the expected isoquinoline in moderate yield after 6 minutes of irradiation.

In contrast with the known base-promoted desulfonylation of *N*-sulfonyl-1,2-dihydroisoquinolines in solution,[13a] when compounds of entries 4–7 were irradiated, poor yields of the corresponding isoquinolines were obtained after comparatively long reaction times. Interestingly, it has been reported the easy conversion of the *N*-benzylsulfonyl dihydroisoquinolines of entries 5 and 6 into isoquinolines when treated with Raney Nickel.[13c]

Not quite unexpectedly, a base-promoted retroaldol-like reaction[20] leading to an isoquinoline with simultaneous dehydroxymethylation was observed when the 1-hydroxymethyl-substituted dihydro- isoquinoline derivative of entry 7 was exposed to microwave irradiation, hoping to promote desulfonylation by assistance from the neighboring carbinolic oxygen. Isoquinolines obtained as shown in entries 1 and 4–7 are known natural produts.[13a,c,19]

Table 2 Synthesis of Isoquinolines by Microwave-Assisted Reaction of *N*-Sulfonyl Dihydro- and Tetrahydroisoquinoline Derivatives with KF Supported on Alumina

Entry	Substrate	Time (s)[a]	Product	Yield (%)[b]
1[c]		30		63[d]
2		60		86[e]
3		360		65
4[c]		210		32[f]
5[c]		180		24[g]
6[c]		210		34[f]
7[c]		600		16[d]

[a] Irradiation time at 490 W in a domestic microwave oven.
[b] Isolated yield after column chromatography.
[c] The resulting isoquinolines are natural products, displaying spectral data in agreement with the literature.[13a,c,19]
[d] Mp 89.5–91 ºC (Lit.[13a] 90–91 ºC; 89–90 ºC).
[e] Mp 112–113ºC (Lit.[13a] 112–113 ºC). Complete decomposition was observed after 420 s of irradiation time.
[f] Mp 118–119 ºC (Lit.[19c] 118–119 ºC).
[g] Mp 125–126 ºC (Lit.[19a] 125 ºC).

Although a complete picture of the mechanism of the reactions leading to isoquinolines remains unclear, it is evident that desulfonylation occurs before the dehydrogenation step; thus, reminiscing the results of Kohno and Yamada,[11c] 3,4-dihydroisoquinolines are selectively produced.

For isoquinoline synthesis from dihydroisoquinolines, the reaction takes place more easily by dehydrogenation of 3,4-dihydro-isoquinolines than by oxidative desulfonylation of the 1,2-dihydro derivatives; the latter reaction is known to successfully occur in solution, being promoted by strong bases.[11c,13a] On the other hand, participation of alumina and fluoride-modified alumina as catalyst in dehydrogenation reactions has been documented;[21] this could contribute to explain the transformation of 3,4-dihydroisoquinolines into the related isoquinolines.

Further analysis of the available examples seems to indicate that the transformation of *N*-sulfonyl tetrahydroisoquinolines into their corresponding 3,4-dihydro- forms and afterwards into isoquinolines is highly successful when the C-1 substituent (carbonyl, phenyl) contributes to the acidity of H-1.

In conclusion, we have developed a rapid, mild and environmentally friendly method for the rapid and selective synthesis of 3,4-dihydroisoquinolines and isoquinolines by microwave irradiation of mixtures of *N*-sulfonyl tetrahydroisoquinolines and 37% potassium fluoride supported on alumina. Good yields of product were obtained when H-1 was acidic enough to allow a facile first step, consisting in an oxidative desulfonylation.

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(22) The selective elaboration of 1-benzoyl-3,4-dihydroisoquinoline and the related 1-benzoylisoquinoline depicted in entry 1 of Table 1 are representative of a typical experimental procedure. The sulfonamide and 37% KF/alumina (10 weight equivalents, prepared as reported by Schmittling and Sawyer[6]) were mixed in a Pyrex test tube and subjected to microwave irradiation (490 W) during 10 s in a domestic microwave oven (Panasonic NN 6556). The solid was allowed to cool to room temperature and washed with CH_2Cl_2 (3 × 10 mL). The combined organic washings were concentrated under reduced pressure and purified by flash-chromatography, affording 1-benzoyl-3,4-dihydroisoquinoline as an oil in 60% yield; IR (film, cm^{-1}): 3056, 2924, 1670, 1448, 1248, 923, 839, 716; ^1H NMR (200 MHz, $CDCl_3$): δ 2.89 (2 H, t, *J* = 7 Hz), 3.98 (2 H, t, *J* = 7 Hz), 7.27–7.60 (7 H, m) and 8.02–8.05 (2 H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ 25.57, 47.28, 126.59, 127.18, 127.82, 128.55, 130.34, 131.64, 133.87 (2C), 135.50, 137.17, 165.34 and 193.81. Increasing the reaction time to 20 s, followed by the same work-up procedure and flash-chromatography furnished 1-benzoylisoquinoline in 56% yield, as a solid mp 74–76 ºC (ref.[14a] 78–79 ºC; ref.[14b] 76–77 ºC; ref.[14c] 76–77 ºC); IR (film, cm^{-1}): 3054, 1669, 1580, 1498, 1448, 1352, 1227, 1247, 1155, 923, 829, 715, 686; ^1H NMR (200 MHz, $CDCl_3$): δ 7.43–7.51 (2 H, m), 7.57–7.65 (2 H, m), 7.71–7.83 (2 H, m), 7.91–7.93 (3 H, m), 8.22 (1 H, d, *J* = 8 Hz) and 8.66 (1 H, d, *J* = 8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 122.57, 126.20, 126.41, 127.08, 128.31, 128.46, 130.74 (2C), 133.65, 136.62, 136.70, 141.14, 156.43 and 194.71.