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A PRACTICAL ROUTE TO QUINOLINES FROM ANILINES†

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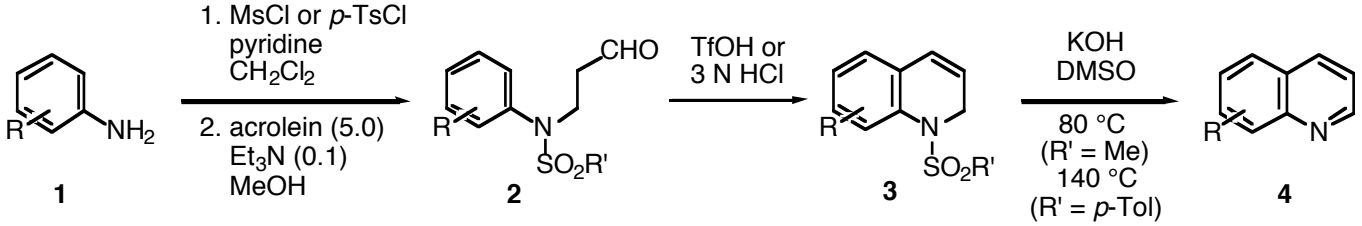
Abstract-A practical route to quinoline from anilines through acid-mediated cyclization of 3-(*N*-aryl-*N*-sulfonylamino)propionaldehydes has been developed. Treatment of the cyclization products, dihydroquinoline intermediates with KOH in DMSO leads to substituted quinolines.

Quinolines represent the major class of heterocycles, and a number of preparations are known to date.[1] The classical Skraup quinoline synthesis is well-known and still frequently used, especially for the synthesis of substituted quinolines.[2] In spite of its generality and versatility, the Skraup synthesis has several considerable drawbacks. First, the reaction usually requires harsh conditions, which makes it tedious to isolate the product from the crude mixture. Second, reaction of *meta*- or 3,4-substituted anilines normally gives a mixture of regioisomers, which are difficult to separate. In the course of our study on the synthesis of indoles from quinolines,[3] we developed a mild and practical synthesis of substituted quinolines. In this communication, we describe a novel route to substituted quinolines from anilines through the acid-mediated cyclization of 3-(*N*-aryl-*N*-sulfonylamino)propionaldehydes (**2**), which can be readily prepared from anilines.

The outline of our protocol is illustrated in Scheme 1. The key intermediate (**2**) were prepared in a straightforward way by treatment of anilines (**1**) with *p*-TsCl/MsCl and pyridine in CH_2Cl_2 at room temperature, followed by Michael addition to acrolein (5 eq) in the presence of Et_3N (0.1 eq) in MeOH (70-100% yields over 2 steps). Cyclization under acidic conditions (*vide infra*) and subsequent treatment with KOH in DMSO give the desired quinolines (**4**).[4]

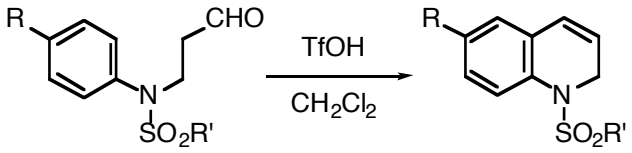


Scheme 1

†This paper is dedicated to Professor Shô Itô on the occasion of his 77th birthday.

In order to investigate the conditions for the cyclization, the reaction of the parent aniline derivative (**2a**) was initially studied. A survey of acids revealed that the expected reaction proceeded smoothly in the presence of TfOH (Table 1, entries 1 and 2).[5] Reaction with other acids such as H_2SO_4, HCl, and TFA resulted in preferential formation of phenylsulfonamide due to retro-Michael reaction. Substrates (**2f-i**) substituted with electron-withdrawing groups were less reactive and necessitated use of one equivalent of TfOH for completion of the reaction (entries 7-10).

Table 1. Cyclization of *p*-Substituted Aniline Derivatives.



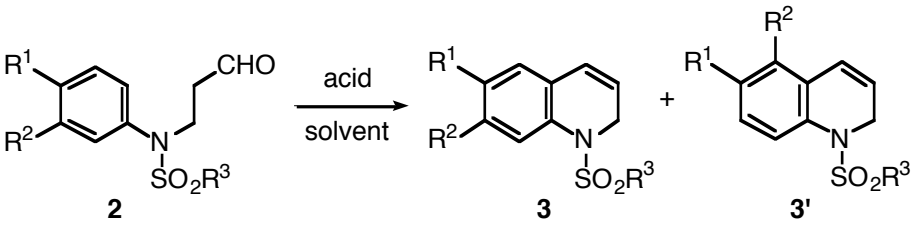
2 **3**

entry	**2**	R	R'	TfOH (eq)	temp (°C)	time (min)	**3**	yield %
1	**2a**	H	Me	1.0	rt	20	**3a**	62
2	**2a**	H	Me	0.1	50	40	**3a**	64
3	**2b**	H	*p*-Tol	0.1	50	60	**3b**	77
4	**2c**	Me	Me	0.1	50	30	**3c**	80
5	**2d**	MeO	Me	0.1	50	60	**3d**	54
6	**2e**	MeO	*p*-Tol	0.1	50	60	**3e**	42
7	**2f**	NO_2	Me	1.0	0	120	**3f**	16
8	**2g**	Cl	Me	1.0	rt	10	**3g**	46
9	**2h**	Br	Me	1.0	rt	20	**3h**	42
10	**2i**	Br	*p*-Tol	1.0	rt	20	**3i**	39

We next turned our attention to the reaction of *meta*- or 3,4-disubstituted aniline derivative (Table 2). Reaction of *m*-methoxy- or *m*-hydroxyaniline derivatives took place smoothly upon heating at 80 °C in 1:1 3N HCl/THF to furnish dihydroquinoline derivative (**3**) with high regioselectivity, while the reaction with TfOH gave a substantial amount of retro-Michael products (entries 1-3). The reaction of 3,4-dimethoxy-, *meta*-bromo-, and 3,4-dichloro-aniline derivatives proceeded with good to excellent regioselectivity under the standard conditions with TfOH (entries 4-7). Sulfonamide moiety slightly influenced on the regioselectivity, and the substrates bearing *p*-toluenesulfonamides generally provided higher regioselectivity.

In contrast to the successful reactions with *para*-, *meta*-, and 3,4-disubstituted aniline derivatives, attempts to cyclize substrates derived from *ortho*-substituted anilines afforded retro-Michael products exclusively (Scheme 2). This may due to difficulty to orient the activated aldehyde moiety and aromatic ring in the same plane because of steric repulsion between the substituent and the sulfonamide.

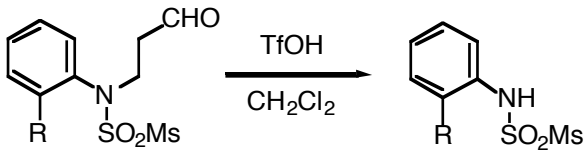
Table 2. Cyclization of *m*- or 3,4-Disubstituted Aniline Derivatives.



2 **3** **3'**

entry	**2**	R^1	R^2	R^3	acid (eq)	solvent	temp (°C)	time (min)	yield %	(**3**/**3'**)[a]
1	**2j**	H	MeO	Me	3 N HCl[b]	THF	80	20	85	8 : 1
2	**2k**	H	MeO	*p*-Tol	3 N HCl[b]	THF	80	40	94	13 : 1
3	**2l**	H	OH	*p*-Tol	3 N HCl[b]	THF	80	20	82	14 : 1
4	**2m**	MeO	MeO	Me	TfOH (0.1)	CH_2Cl_2	50	10	84	1 : 0
5	**2n**	H	Br	Me	TfOH (1.0)	CH_2Cl_2	rt	10	88	3 : 1
6	**2o**	H	Br	*p*-Tol	TfOH (1.0)	CH_2Cl_2	rt	10	85	5 : 1
7	**2p**	Cl	Cl	Me	TfOH (1.0)	CH_2Cl_2	rt	10	36	2 : 1

[a]Ratio was determined by ^{1}H NMR analysis of the crude product. [b]1:1 (v/v) 3N HCl/THF was used.



Scheme 2

The practical utility of this method has been proven by its application for the large scale preparation of 7-methoxyquinoline. After conversion of *m*-anisidine (52.3 g) to the corresponding *p*-toluenesulfonamide (*p*-TsCl, Na_2CO_3, 1,4-dioxane/H_2O, rt, 30 min), Michael addition to acrolein led to the key intermediate (**2k**) (acrolein, Et_3N, MeOH, 0 °C to rt, 10 min). Heating the mixture at reflux in 1:1 3N HCl/THF for 15~30 min afforded the dihydroquinoline (**3k**/**3'k**), and subsequent treatment with KOH/DMSO (140 °C, 30 min) furnished the desired 7-methoxyquinoline (43.4 g, 63% yield, 4 steps) containing 4-10% of 5-methoxyquinoline. No purification was necessary to carried out the sequence. Pure 7-methoxyquinoline was obtained by recrystallization of its nitric acid salt and treatment with base.

In conclusion, we have developed a novel route to quinoline from anilines, featuring the acid-mediated cyclization of 3-(*N*-aryl-*N*-sulfonylamino)propionaldehydes (**2**) and subsequent base-induced conversion to quinolines. This methodology may serve as a mild and practical route to quinolines.

REFERENCES AND NOTES

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2. R. H. F. Manske and M. Kulka, *Organic Reactions*, 1953, **7**, 59.
3. H. Tokuyama, T. Yamashita, M. T. Reding, Y. Kaburagi, and T. Fukuyama, *J. Am. Chem. Soc.,* 1999, **121**, 3791.
4. The reaction mechanism of this conversion may be either basic hydrolysis of sulfonamide and subsequent air oxidation to quinolines or β-elimination of the sulfonyl group to furnish quinolines directly. **Representative procedure.** A mixture of dihydroquinoline intermediate (**3d**) (36.4 mg, 0.152 mmol) and KOH (34.2 mg, 0.610 mmol) in DMSO (1.5 mL) was heated to 80 °C. After heating for 30 min, the reaction mixture was partitioned between Et_2O and water. The aqueous layer was extracted with Et_2O twice. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purification by preparative thin layer silica gel chromatography (40% EtOAc in hexanes) afforded 6-methoxyquinoline (22.5 mg, 93%). IR (film, cm^{-1}): 2959, 1623, 1596, 1500, 1378, 1229, 834. ^1H NMR (400 MHz, $CDCl_3$): δ 3.93 (s, 3H), 7.07 (d, *J* = 2.7 Hz, 1H), 7.33-7.39 (m, 2H), 8.00 (d, *J* = 9.3 Hz, 1H), 8.04 (d, *J* = 8.3 Hz, 1H), 8.76 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.5, 105.1, 121.3, 122.2, 129.3, 130.8, 134.7, 144.4, 147.9, 157.7. These spectral data were identical with those of the commercial compound. The reaction of the corresponding *p*-toluenesulfonamide derivatives was carried out at 140 °C.
5. **Representative procedure.** To a CH_2Cl_2 (2.0 mL) solution of **2c** (104 mg, 0.432 mmol) was added TfOH (3.8 μL, 0.043 mmol) at rt. The resulting mixture was stirred at 50 °C for 20 min. The reaction mixture was diluted with EtOAc and washed with sat. $NaHCO_3$. The aqueous layer was extracted with EtOAc twice. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purification of the crude product by preparative thin layer silica gel chromatography (40% EtOAc in hexanes) afforded the desired dihydroquinoline derivative (**3c**) (78 mg, 80%). IR (film, cm^{-1}): 2930, 1490, 1346, 1336, 1158, 1065, 964, 824, 760. ^1H NMR (400 MHz, $CDCl_3$): δ 2.34 (s, 3H), 2.69 (s, 3H), 4.39 (m, 2H), 6.00-6.03 (m, 1H), 6.57 (d, *J* = 10.0 Hz, 1H), 6.96 (s, 1H), 7.08 (d, *J* = 8.0 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.9, 37.5, 45.4, 124.6, 126.4, 127.1, 127.4, 128.8, 129.1, 136.8. HR-MS (EI) Calcd for $C_{11}H_{13}NO_2S$: 223.0667. Found. 223.0664.