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Selective Hydrogenation of 9-Aminoacridine over Supported Noble Metal Catalysts

Kinya SAKANISHI, Isao MOCHIDA,* Hiroshi OKAZAKI,† and Mahito SOEDA†
Institute of Advanced Material Study, Kyushu University, Kasuga, Fukuoka 816
†R & D Laboratories, Nippon Steel Chemical Co., Tobata, Kitakyushu 804

The selective hydrogenation of 9-aminoacridine(1) into 1,2,3,4-tetrahydro-derivative(2) was searched using noble metal catalysts(Pd, Rh, Pt, and Ru) at around 80 °C and 60 atm of H_2. The Pd/Al_2O_3 catalyst was found most selective to produce 2 in a higher yield of 60% at a conversion of 97%. The hydrogenation pathway of 1 is discussed in comparison with that of acridine.

Selective hydrogenation of nitrogen-containing polyaromatic hydrocarbons derived from coal tar is an efficient route to prepare the intermediates for functional molecules and medicines.[1-5] The present authors established the selective partial hydrogenation of acridine and isoquinoline, selecting noble metal catalysts and reaction conditions.[6-9]

In the present study, the selective synthesis of 1,2,3,4-tetrahydro-9-aminoacridine 2 (called THA in the pharmacy), an expected remedy for Alzheimer-like senile dementia at the recent clinical stage,[10] was studied using 9-aminoacridine 1 as a starting chemical. Its high selectivity and the other products' distribution were tried to control because its high yield may allow easy purification very essential for its medical use. The reaction profile of its hydrogenation on noble metals and influences of amino group were also objectives for the present study.

9-aminoacridine 1 (99% purity containing 1% of its hydrochloric salt) and ethanol(reaction solvent) used in the present study were commercially available reagents of guaranteed grade. Commercial noble metal catalysts of Pd, Pt, Rh, and Ru on alumina and Pd on carbon(Metal content: 5 wt%), supplied from Engelhalt Co., were used without any pretreatment.

A mixture of 1 (5 g), ethanol(150 ml) and the catalyst(0.5 g) was charged into an autoclave of 300 ml capacity. After the complete replacement of atmosphere in the autoclave with hydrogen flow, the hydrogenation was carried out at 80 °C or 100 °C for 2 h or 15 min, respectively. The initial pressure of H_2 was 60 atm at room temperature. The reaction mixture was recovered by washing with ethanol, and the catalyst was filtered off. After distilling out the solvent, crude products were separated by a column chromatograph using an activated alumina. The isolated products were identified by GC-MS and ^{1}H-NMR.

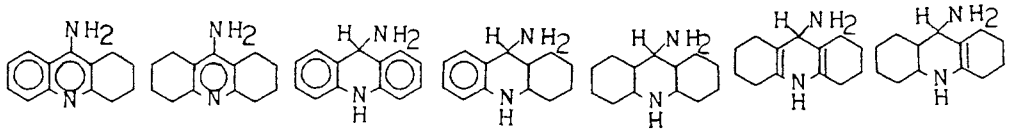
Table 1 summarizes the conversion and selectivity in the hydrogenation of

Table 1. Hydrogenation of 1 under various conditions

Catalyst	Conditions[a]	Conversion	Selectivity/%[b]					
	(°C-atm-h)	%	[2]	[3]	[4]	[5]	[6]	others
Pd/Al_2O_3	80-60-2	97	60	5.2	4.3	0.0	3.4	27
Pd/C	80-60-2	93	54	14	14	0.0	2.9	15
Rh/Al_2O_3	80-60-2	99	32	21	0.1	0.0	19	28
Pt/Al_2O_3	80-60-2	68	49	5.1	45	0.0	0.0	0.9
Ru/Al_2O_3	80-60-2	55	58	10	31	0.0	0.0	0.8
Pd/Al_2O_3	80-60-2	97	60	5.2	4.3	0.0	3.4	27
Pd/Al_2O_3	80-50-1	99	51	6.8	0.2	0.0	23	19

a) Reaction temperature - initial pressure of H_2 - reaction time.

b)



2 3 4 5 6 others

1 on various noble metal catalysts at 80 °C for 2 h. The Pd/Al_2O_3 catalyst exhibited the highest selectivity of 60% for 2 at a conversion as high as 97 %. The Pd/C catalyst showed a little lower conversion of 93% as well as selectivity of 54% for 2. The Rh/Al_2O_3 catalyst converted 1 almost completely, however the selectivity for 2 was rather poor (32%) with increasing the selectivities for the more extensively hydrogenated products of 3, 6, and others. No definite selectivity was found in these products(19 - 28%). The Pt and Ru catalysts showed much lower activities at the conversions of 68 and 55%, respectively. The Ru/Al_2O_3 showed a high selectivity for 2 (58%). These

catalysts were marked to produce a large amount of dihydro-derivative of 4 (45 and 31% respectively) which may be unstable under the GC-MS conditions.

The conversion of 1 increased up to ca. 100% with a little decrease of 2 in the two-stage hydrogenation using the Pd/Al_2O_3 catalyst at both stages under the reaction conditions of 80 °C, 60 atm, 2 h for the first stage and 80 °C, 50 atm, 1 h for the second stage, respectively, achieving over 98% purity of 2 purifying with an activated alumina in a column chromatograph, and successively recrystallization in 50/50 v/v% ethanol/acetone solvent. The two-stage hydrotreatment was found to provide a product distribution suitable for the purification of 2 by hydrogenating sufficiently the starting material which is difficult to separate from 2.

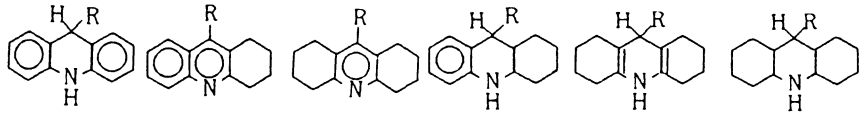
The hydrogenation reactivities of 1 and acridine are compared under the same conditions of 100 °C, 70 atm, and 15 min to be summarized in Table 2. The

Table 2. Comparison of 1 and acridine in their hydrogenation reactivity and product selectivity

Substrate	Catalyst	Conditions[a]	Conversion	Selectivity/%[b]						
		(°C-atm-min)	%	2H	4H	8HA	8HA'	10HA	PHA	others
acridine	Pd/Al_2O_3	100-70-15	94	85	0.9	2.0	6.5	-	1.7	4.0
	Rh/Al_2O_3	100-70-15	92	26	13	29	9.3	-	15	7.9
	Pt/Al_2O_3	100-70-15	87	79	1.7	5.0	4.9	-	2.3	7.2
1	Pd/Al_2O_3	100-70-15	61	0.0	67	18	-	8.2	3.2	3.6
	Rh/Al_2O_3	100-70-15	72	0.0	35	27	-	22	18	0.0
	Pt/Al_2O_3	100-70-15	45	5.8	43	2.0	-	0.1	0.1	49

a) Reaction temperature-initial pressure of H_2-reaction time.

b) Hydrogenated products(R=H for acridine, R=NH_2 for 1)
others for acridine: unidentified products,
others for 1 : mainly 9,10-dihydroacridine and trace of acridine



2H 4H 8H 8H' 10H PH

product distribution from 1 at 100 °C was much the same to that at 80 °C as is shown in Table 1, although the conversions were kept rather low at the former

temperature because of the shorter reaction time. The slightly higher selectivity for 2 was marked on the Pd/Al_2O_3 catalyst at a higher temperature and a shorter reaction time. A significant amount of deaminated products(mainly 9,10-dihydroacridine and trace of acridine) was produced on the Pt/Al_2O_3 catalyst at this temperature.

Acridine was more readily hydrogenated to obtain the conversions over 85% on all the catalyst, while the order of catalytic activity was found same, Rh > Pd > Pt, with both substrates. The selectivity for the dihydro-derivative was much higher in the hydrogenation of acridine than that of 1, inicating steric hindrance of the amino group at the position 9, which is most reactive according to their highest Frontier electron densities(Fr). As observed with 1, the substituent group at the position 9 enhanced the hydrogenation of the external ring, where the π-bond order is highest but less reactive in terms of Fr, hence the selectivity for the tetrahydro-derivative was much lower from acridine. Similar effects have been reported with alkyl groups at the position 9.[11]

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