Activation of Reducing Agents. Sodium Hydride Containing Complex Reducing Agents. 13.[1] Selective Heterogeneous Hydrogenation of Polyfunctional Substrates over Nic

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Preparative-scale heterogeneous hydrogenations over Nic at room temperature and 1 atm are described. It is shown that these catalysts allow the selective hydrogenation of carbon–carbon double bonds in the presence of oxo groups without side reactions. Alkynes and functional alkynes are selectively hydrogenated to the corresponding cis alkenes in high yields. Carbonyl group hydrogenations were also performed in high yields. Selective hydrogenation properties of Nic were exemplified in the steroid series. Finally, it was demonstrated that this new catalyst-preparation concept is not limited to nickel and also applies to the preparation of cobalt and palladium catalysts.

In the preceding paper,[1] we have described the basic study which has to be done when new catalysts, such as Nic, are devised. However, this kind of study was, as usual, performed on monofunctional substrates, and quantitative results were obtained by GLC analysis.

As the picture obtained for Nic was fairly good, it was highly necessary to complete this information by a study of polyfunctional substrate hydrogenations with isolated-yield data.

Thus, with the intent of proving that Nic are highly selective and convenient catalysts, we undertook a survey of hydrogenations under model synthetic conditions.

Results and Discussion

During the present work, two kinds of Nic were used (see Experimental Section). One was the Nic described in the preceding paper.[1] The other was the catalyst obtained by simple washing of Nic with EtOH to get rid of the soluble alkoxide: we shall refer to it as Nic_w.

Hydrogenation of Functional Alkenes. The presence of a functional group in an alkene may pose a problem for the selective hydrogenation of the carbon–carbon double bond. For example, the presence of heteroatoms, such as nitrogen, may lead to many side reactions;[2] hydrogenolysis of allylic or benzylic alcohols may also occur.[3] Furthermore, simultaneous reduction of the functional group and the carbon–carbon double bond must be avoided. Finally, the presence of a functional group may prevent hydrogenation of the double bond.[4]

With these preoccupations in mind, hydrogenations of representative functional alkenes over Nic or Nic_w were performed. In all cases, hydrogenations were stopped after absorption of 1 equiv of hydrogen. The main results are reported in Table I.

These data deserve some comments. First, it is clear that these catalysts may be used for the hydrogenation of carbon–carbon double bonds even if different functional groups are present in the substrate. The high yields and purities of the isolated products show that little, if any, side reaction occurred (particularly, no hydrogenolysis was observed). Second, it is noteworthy that carboxyl groups (as sodium salts) do not prevent hydrogenations over Nic. Note that cinnamic acid could not be reduced over P_2 nickel.[5] On the contrary, P_2 nickel allows hydrogenation of unsaturated nitriles to saturated ones[6] whereas Nic (unreported results) do not lead to selective hydrogenations. Finally, the case of 6-methylhept-5-en-2-one illustrates the limitation of Nic. Indeed, when the ethylenic moiety is too much hindered and not conjugated with a carbonyl group,[7] selective hydrogenation becomes more difficult. However, it must be noted that, even in this difficult case, Nic_w in EtOH led to 50% selective hydrogenation of the double bond. It is noteworthy that changing Nic_w for Nic, and EtOH for hexane, led to selective hydrogenation of the carbonyl group.

Semihydrogenation of Alkynes and Functional Alkynes. Selective semihydrogenation of alkynes is a very important problem,[8] often encountered during the synthesis of natural products. Literature data indicate that many catalysts have been proposed to solve this problem.[4] However, while some of them lead to rather high selectivities with disubstituted alkynes, much less satisfactory results are often obtained when functional groups are present[9] or when 1-alkynes are considered.[10]

To test the Nic possibilities in this area, we tentatively performed selective semihydrogenations of alkynes (Table II). In most cases, quinoline was used to increase the Δ value,[11] thus more easily allowing the obtaining of the maximum yield of semihydrogenated product. From a practical viewpoint, if no preliminary analytical study can be made, the following procedure is recommended: hydrogenations of disubstituted alkynes must be stopped just after the uptake of 1 equiv of hydrogen. On the contrary, hydrogenations of 1-alkynes must be stopped only after

(1) For part 12, see J. J. Brunet, P. Gallois, and P. Caubere, *J. Org. Chem.*, preceding paper in this issue. This work together with part 12 represents part of the research work of P. G. for his "these de Docteur-Ingénieur".

(2) See, for examples, E. B. Maxted and A. G. Walker, *J. Chem. Soc.*, 1094 (1948); W. H. Hartung and R. Simonoff, *Org. React.*, 7, 263 (1953).

(3) See, for example, P. N. Rylander, "Catalytic Hydrogenation over Platinium Metals", Academic Press, New York, 1967.

(4) M. Friefelder, "Practical Catalytic Hydrogenation", Wiley-Interscience, New York, 1971. See also ref 5 in which it is reported that cinnamic acid was not hydrogenated over nickel boride.

(5) T. W. Russell and R. C. Hoy, *J. Org. Chem.*, **36**, 2018 (1971).

(6) T. W. Russell, R. C. Hoy, and J. E. Cornelius, *J. Org. Chem.*, **37**, 3552 (1972).

(7) Highly selective semihydrogenation of the carbon–carbon double bond of mesityl oxide over Nic has been described in the preceding paper.[1]

(8) E. N. Marvell and T. Li, *Synthesis*, 457 (1973).

(9) See, for example, G. F. Hennion and R. S. Hanzel, *J. Am. Chem. Soc.*, 82, 4908 (1960); M. Gouge, *Ann. Chim. (Paris)*, 6(12), 648 (1951), and references cited therein.

(10) See, for example, L. K. Freidlin and Y. Y. Kaup, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 166 (1963).

(11) Δ represents the ratio of hydrogen uptake before and after the maximum percent of semihydrogenation products are obtained. Quinoline was used to increase these Δ values. Moreover, if the reaction is stopped too late, the presence of quinoline prevents cis–trans isomerization.

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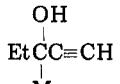
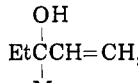
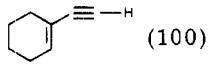
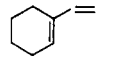
Table I. Hydrogenation of Functional Alkenes over Nic or Nic_W at 25 °C (1 atm)

substrate (mmol)	catalyst[a]	solvent (mL)	t	hydrogenation product	isolated yields, %	purity,[b] %
allylamine (20)	Nic_W	MeOH (20)	22 min	propylamine[c]	95	100
ethyl crotonate (10)	Nic_W	MeOH (15)	21 min	ethyl butyrate	*d*	100
trans-cinnamyl alcohol (10)	Nic_W	EtOH (15)	25 min	3-phenylpropanol	92	100
trans-cinnamaldehyde (10)	Nic_W	EtOH (15)	95 min	3-phenylpropanal	83	100
benzalacetone (10)	Nic_W	EtOH (15)	12 min	1-phenyl-3-butanone	94	100
isophorone (100)	Nic_W	EtOH (50)	21 min	3,3,5-trimethylcyclohexanone	86	98
6-methylhept-5-en-2-one (10)	Nic_W	EtOH (15)	11 h	6-methylhept-5-en-2-one		15[e]
				6-methylheptan-2-one		50[e]
				6-methylhept-5-en-2-ol		20[e]
				6-methylheptan-2-ol		15[e]
6-methylhept-5-en-2-one (10)	Nic	hexane (15)	20 h	2-methylhept-2-en-6-ol	90	100
cinnamic acid (10)	Nic	EtOH[f] (15)	58 min	3-phenylpropionic acid	97	100

[a] Ratio of catalyst/reactant of 1/20 (in moles) except for allylamine (1/40) and cinnamaldehyde (1/10). [b] Determined by GLC analysis on capillary columns. [c] Isolated as the hydrochloride. [d] Unisolated from the solvent. [e] Determined by GLC analysis with internal standards. [f] In this case 10 mL of 1 N NaOH was added to the reaction mixture.

Table II. Selective Semihydrogenation of Alkynes over Nic or Nic_W at 25 °C (1 atm)

substrate (mmol)	catalyst[a]	solvent[b] (mL)	semihydrogenation product	isolated yields, %	purity,[c] %
PrC≡CMe (100)	Nic_W	MeOH (50)	PrCH=CHMe (cis)	82	96
EtC≡CEt (100)	Nic_W	MeOH (50)	EtCH=CHEt (cis)	80	97
PhC≡CMe (10)	Nic_W	EtOH (15)	PhCH=CHMe (cis)	80	90
$Et_2NCH_2C{\equiv}CEt$ (20)	Nic_W	MeOH (20)	$Et_2NCH_2CH{=}CHEt$ (cis)	93[d]	97
$HOCH_2C{\equiv}CCH_2OH$ (25)	Nic	EtOH (20)	$HOCH_2CH{=}CHCH_2OH$ (cis)	80	95
PhC≡CH (100)	Nic	EtOH (50)	$PhCH{=}CH_2$	86	91
$Et_2NCH_2C{\equiv}CH$ (20)	Nic_W	MeOH (20)	$Et_2NCH_2CH{=}CH_2$	90[d]	90
 (100)	Nic	EtOH (50)		90	81
 (100)	Nic	MeOH (50)		84	80

[a] Ratio of catalyst/reactant of 1/50 (in moles), except for 2-butyne-1,4-diol for which a ratio of 1/5 was used. [b] In all cases, except that for the aminoalkynes, quinoline (0.2 mL for 10 mmol of substrate) was added. [c] Determined by GLC analysis on capillary columns. In most cases, the impurity was the fully saturated product. [d] Isolated as the hydrochloride.

the uptake of 1.2 equiv of hydrogen.[12]

From the overall data, it appears that Nic may be considered among the more selective heterogeneous catalysts described in the literature. Indeed, they are nearly equivalent (although slightly less efficient) to P_2 nickel[13] for the selective semihydrogenation of disubstituted alkynes.[14] Concerning functional alkynes, such as (diethylamino)pent-2-yne and 2-butyne-1,4-diol, there are no P_2 nickel data for the first and only total hydrogenation data for the latter.[5] The very high selectivity of Nic is well demonstrated by the results obtained with 2-butyne-1,4-diol. Indeed, selective hydrogenation to pure *cis*-2-butene-1,4-diol has been reported as difficult, leading either to numerous side products or to a nonnegligible percent of *trans*-2-butene-1,4-diol.[15] Note that Lindlar palladium[16] is not the catalyst of choice for this selective semihydrogenation.[17] Once again, it is noteworthy that no hydrogenolysis was observed over Nic.

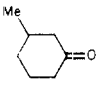
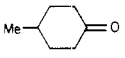
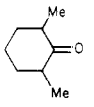
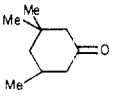
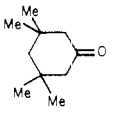
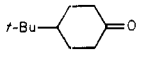
Semihydrogenations of 1-alkynes are demonstrative of the efficiency of Nic. Particularly, the result obtained with 1-ethynylcyclohexene compares favorably with those obtained over Lindlar palladium,[8,18] taking into account that in the present work yields refer to isolated products.

Hydrogenation of Carbonyl Compounds. As briefly noted in the preceding paper,[1] one of the most interesting properties of Nic is their aptitude to promote hydrogenation of carbonyl compounds under ambient conditions.

A more complete study of this property was undertaken and hydrogenation of some representative ketones and aldehydes performed. The main results are summarized in Table III. As for ethylenic unsaturations, Nic are very sensitive to the steric hindrance about the carbonyl groups. However, it is clear that these catalysts are very convenient for preparative-scale hydrogenations of carbonyl compounds at 25 °C (1 atm). Indeed, as previously noted,[1] the other nickel catalysts active for carbonyl hydrogenation (W_7, W_6, promoted W_4) are much less convenient than Nic, owing to either their instability on storage or their so-

(12) The basic analytical studies reported in ref 1 indicate that the maximum selectivity for 1-alkyne hydrogenations over Nic was obtained after uptake of 1.2 equiv of hydrogen.
(13) C. A. Brown and V. K. Ahuja, *J. Org. Chem.*, 38, 2226 (1973), and references cited therein.
(14) C. A. Brown and V. K. Ahuja, *J. Chem. Soc., Chem. Commun.*, 553 (1973).
(15) See, for example, R. Romanet, *C. R. Hebd. Seances Acad. Sci.*, **236**, 1044 (1953), and references cited therein.
(16) H. Lindlar, *Helv. Chim. Acta*, 35, 446 (1952).
(17) R. J. Tedeschi and G. Clark, Jr., *J. Org. Chem.*, 27, 4323 (1962).
(18) E. N. Marvell and J. Tashiro, *J. Org. Chem.*, 30, 3991 (1965).

Table III. Hydrogenation of Carbonyl Derivatives (10 mmol) over Nic[a] in EtOH (15 mL) at 25 °C (1 atm)

carbonyl compd	initial rate, cm^3/min	$t_{100\%}$, h	isolated alcohol yield, %	isomer comp,[b] %
n-BuCO-*n*-Bu	1.3	9	88	
$PhCOCH_3$	5.3	2.5	92	
	3.3	2.75	81	
	2	4.5	83	70 cis, 30 trans
	3	4.2	82	48 cis, 52 trans
	2.3	3.8	82	52 cis, 48 trans
	0.65	16	85[c]	54 cis-cis, 36 cis-trans, 10 trans-trans
	1.5	6	88[d]	5 cis, 95 trans
	0.7	16	90	-
	0.6	20	94	85 cis, 15 trans
	3	4	92	55 cis, 45 trans
PhCHO	5	1.6	91	
$CH_3(CH_2)_5CHO$[e]	1	14	88	

[a] Ratio of catalyst/reactant of 1/20 (in moles). [b] Determined by GLC analysis at the end of the reaction. [c] The cis-cis and cis-trans isomers were isolated in pure state in 42 and 27% yield, respectively. [d] The trans isomer could be isolated pure in 85% yield. [e] In this case, a Nic_W was used with Et_3N (1 mL) with a catalyst/substrate ratio of 1/10.

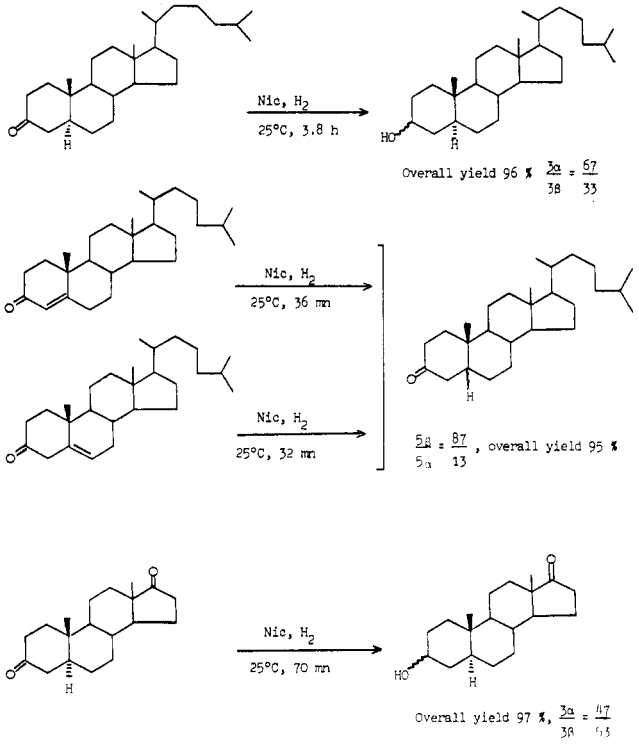
phisticated preparation.[4] On the other hand, Nic are much more active for carbonyl compound reduction than the easily prepared nickel borides.[19]

Concerning the stereochemistry of the reduction, it was beyond the scope of the present work to fully study the conditions allowing stereospecific hydrogenations. However, a rapid examination led us to interesting observations: for example, hydrogenation of 4-*tert*-butylcyclohexanone in DMF led to 4-*tert*-butylcyclohexanols in a cis/trans ratio of 66/34 whereas the same reaction conducted in *i*-PrOH led to the ratio 40/60. Variation of the activating alkoxide also led to variation of the stereoselectivity: thus, in EtOH, $Et(OCH_2CH_2)_2ONa$ led to a cis/trans ratio of 43/57 whereas $Me_2C(ONa)(CH_2)_2CMe_2ONa$ led to a ratio of 63/47. Thus, it may be conjectured that it should be possible to direct the stereoselectivity by varying the solvent or the activating alkoxide. This possibility is currently under investigation.

It was decided to study some examples of preparative-scale hydrogenations of some much more sophisticated substrates. Among the numerous possibilities, some keto steroids were selected (see Scheme I).

These data show that Nic are still very convenient catalysts, leading to quantitative overall yields. Moreover, their potential selectivity is well demonstrated. Indeed, hydrogenation of Δ^4- and Δ^5-3-cholestenone led to a mixture of 5α- and 5β-3-cholestanone in a 13/87 ratio, thus

Scheme I. Hydrogenation of 3-Keto Steroids (2.5 mmol) over Nic (0.25 mmol)[a]



[a] In THF-EtOH (1/1) at room temperature, 1 atm, and 2500 revolutions/min.

(19) S. Mitsui, H. Saito, Y. Yamashita, M. Kaminaga, and Y. Senda, *Tetrahedron*, **29**, 1531 (1973); T. W. Russel, D. M. Duncan, and S. C. Hansen, *J. Org. Chem.*, **42**, 551 (1977).

exhibiting a high selectivity for the formation of the A–B cis-fused-ring product (5β isomer). Note that similar results have been reported with palladium catalysts in EtOH.[20]

Moreover, highly selective hydrogenation of the less hindered carbonyl group of 5α-androstane-3,17-dione confirms the dramatic sensitivity of Nic to the nature and environment of carbonyl groups. Thus, Nic must be recommended for selective hydrogenation of such polycarbonyl compounds.

Conclusion

The present work completes the data reported in the preceding paper on Nic properties. These new catalysts are very convenient for carbon–carbon double bond hydrogenations and are convenient overall for triple bond selective semihydrogenations on a *preparative scale*. Interestingly, Nic also promote hydrogenation of carbonyl compounds under ambient conditions. Furthermore, selective hydrogenation of the carbon–carbon double bond of unsaturated ketones may be easily achieved as well as selective hydrogenation of certain polycarbonyl compounds. Thus, the use of these new, cheap, very active, and selective nickel catalysts is highly recommended for preparative-scale hydrogenation in organic synthesis. It may be conjectured that, as for complex reducing agents,[21] a large variety of catalysts should be obtained by varying the metal salt.

Preliminary experiments conducted in this aim with Coc and Pdc (Co and Pd catalysts prepared as were Nic, from $Co(OAc)_2$ and $Pd(OAc)_2$, respectively) led to promising results. Indeed, it was found that Coc, although less active than Nic, promote hydrogenation of alkenes, alkynes under ambient conditions, and carbonyl compounds at 25 °C under low pressure (5 atm). It was also shown that selective hydrogenation of mesityl oxide (10 mmol) to methyl isobutyl ketone over Pdc (0.25 mmol) was very easily performed. Indeed, hydrogen uptake abruptly stopped after absorption of 1 equiv of H_2 (20 min). GLC analysis indicated 100% purity of methyl isobutyl ketone. Furthermore, hydrogenation of 3-methylpent-1-yn-3-ol (10 mmol) over Pdc (0.25 mmol) yielded pure 3-methylpent-1-en-3-ol in 100% absolute yield (GLC analysis with internal standards) at $t_{50\%}$ = 7 min. However, under the conditions used here, no noticeable breakdown of the hydrogenation curve was observed. This result indicates that, contrary to nickel catalysts, Pdc do not promote hydrogenation without desorption of the alkene, thus allowing highly selective reduction. Thus, it should be conjectured that Pdc will be better catalysts than Nic for some selective hydrogenations, and this possibility is currently being studied. However, it must be borne in mind that, owing to the special properties of Nic, the potential advantages of Pdc will not compensate their expense in every case.

Finally, it must be concluded that, as expected, complex reducing agents constitute a new source of numerous active and selective heterogeneous hydrogenation catalysts.

Experimental Section

Materials. Fluka sodium hydride (50–60% in oil) was used and washed several times with THF in the reaction flask under nitrogen. Badische Anilin reagent-grade THF was distilled from benzophenone–sodium couple before use. (The absence of peroxides was tested for before each run.) Prolabo nickel acetate was dried under vacuum for 16–20 h at 100–110 °C and stored in a vacuum desiccator with P_2O_5 filling, as were $Pd(OAc)_2$ and $Co(OAc)_2$. Activating alcohols were distilled from sodium. All chemicals either were commercial (Fluka or Aldrich) or were prepared by classical procedures. They were purified either by distillation, by recrystallization, or by column chromatography before use. Hydrogenation solvents were purified by classical procedures.[1] Nitrogen R, argon U, and hydrogen (L'Air Liquide) were used.

General Methods. GLC analyses were performed on a Girdel 300, Girdel 3000, or Carlo-Erba GI 452 apparatus (flame ionization) equipped with squalene, Carbowax 20-M, and OV-101 capillary columns (50 m) or 5 m × $^1/_8$ in. columns packed with 15% UCON 50 HB 2000 on Chromosorb P (80–100 mesh).

IR spectra were recorded with a Perkin-Elmer 457 spectrometer and NMR spectra with a Perkin-Elmer R 12 instrument. Nickel titrations were performed with a Varian Techtron atomic absorption photometer (Model 1200) used at 352.4 nm. Preparative liquid chromatography was performed on silica either with Merck Lobar type B columns or with Waters Prep 500 columns with ether–petroleum ether or hexane–ethyl acetate mixtures as eluent.

Preparation and Storage of Catalysts. Unless otherwise specified, catalysts were prepared from *t*-AmONa as activating alkoxide. Sodium hydride (60 mmol) was placed under nitrogen into a four-necked flask equipped with a cold condenser, a thermometer, a dropping funnel, and a mechanical stirrer. After being washed three times with anhydrous THF, sodium hydride was covered with 20 mL of THF. Nickel acetate (10 mmol) and THF (5 mL) were then successively added to the stirred suspension. After the mixture was heated to 45 °C, *t*-AmOH (20 mmol) in 5 mL of THF was added dropwise. A black coloration rapidly developed. After being stirred for 3 h at 45 ° C, the reaction medium was allowed to cool to room temperature. The catalyst suspension was then syringed and stored under argon in a two-necked flask (equipped with two stopcocks) in which was placed a magnetic stirrer. For each run, after a short period of stirring, the catalyst (1.5 mL = 0.5 mmol of Ni) was syringed through one stopcock while argon was introduced through the other.

Hydrogenation Apparatus and General Procedure. The hydrogenation apparatus and the general procedure for hydrogenations over Nic were described in the preceding paper.[1] For hydrogenations over Nic_w, the following pretreatment was used. After addition of the catalyst suspension to 10 mL of EtOH in the hydrogenation vessel, the black powder was washed three times with 10 mL of EtOH under hydrogen, with 0.5 min of stirring between each washing. Then Nic_w was ready for use, and the classical procedure was used.[1]

For preparative-scale hydrogenation conducted with 0.1 mmol of substrate, the hydrogenation vessel was cooled with a water bath to avoid too large a temperature increase.

Hydrogenations of Functional Alkenes (Table I). The experiments were stopped after absorption of 1 equiv of hydrogen. For hydrogenation over Nic, the following workup was used. After filtration, the catalyst was rinsed with diethyl ether. The filtrate was then added to 20 mL of water, acidified with 2 N HCl, and extracted with diethyl ether. The organic phase was dried over $MgSO_4$. After distillation of the solvents at atmospheric pressure, the hydrogenation products were purified by silica column chromatography. For hydrogenations over Nic_w, the filtrate was simply evaporated at atmospheric pressure, and the hydrogenation products were purified as above. In the case of propylamine, the hydrochloride was obtained by stirring the filtrate under a dry HCl atmosphere.

Isolated compounds were identified by comparison of their physical and spectroscopic properties with those described in the literature. In most cases, direct comparison with authentic samples was possible. The purities were determined by GLC analysis.

Semihydrogenation of Alkynes (Table II). The experiments were stopped after the predetermined hydrogen uptake had been reached (see previous text).

For simple alkynes and for 2-butyne-1,4-diol, the following workup was used. After filtration, the catalyst was rinsed with pentane, and the filtrate was poured on water (20 mL) and acidified with 2 N HCl. After the mixture was extracted with

(20) R. L. Augustine, *Adv. Catal.*, **25**, 56 (1976), and references cited therein.

(21) P. Caubere, *Top. Curr. Chem.*, **73**, 50 (1978); J. J. Brunet, R. Vanderesse, and P. Caubere, *J. Organomet. Chem.*, **157**, 125 (1978).

pentane and the extract dried over $MgSO_4$, the solvents were removed at atmospheric pressure. The hydrogenation products were obtained by distillation. *cis*-2- and *cis*-3-hexenes were obtained by distillation with a Nester-Faust NFT 50 spinning-band column.

In the case of functional alkynes, except the amino ones, the hydrogenation products were extracted with diethyl ether instead of pentane and then treated as above.

In the case of aminoalkynes, the filtrate was treated as for propylamine (vide supra). The crude hydrochloride was then purified by dissolving it in the minimum amount of acetone and then precipitating it with diethyl ether.

Isolated compounds were identified by comparison of their spectroscopic properties with those described in the literature. In some cases, direct comparison with authentic samples could be done. The purities were determined by GLC analysis.

Hydrogenation of Carbonyl Compounds (Table III). At the end of the reaction, the catalyst was filtered and rinsed with dichloromethane. After addition of water, the filtrate was acidified with 2 N HCl, extracted with dichloromethane, and dried over $MgSO_4$. After removal of the solvents, the hydrogenation products were separated by silica column chromatography. In the case of keto steroids (Scheme I), chloroform was used instead of dichloromethane.

Isolated compounds were identified by comparison of their physical and spectroscopic properties with those described in the literature. In most cases direct comparison with authentic samples was achieved.

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Registry No. Allylamine, 107-11-9; ethyl crotonate, 10544-63-5; *trans*-cinnamyl alcohol, 4407-36-7; *trans*-cinnamaldehyde, 14371-10-9; benzalacetone, 122-57-6; isophorone, 78-59-1; 6-methylhept-5-en-2-one, 110-93-0; cinnamic acid, 621-82-9; propylamine hydrochloride, 556-53-6; ethyl butyrate, 105-54-4; 3-phenylpropanol, 122-97-4; 3-phenylpropanal, 104-53-0; 1-phenyl-3-butanone, 2550-26-7; 3,3,5-trimethylcyclohexanone, 873-94-9; 6-methylheptan-2-one, 928-68-7; 6-methylhept-5-en-2-ol, 1569-60-4; 6-methylheptan-2-ol, 4730-22-7; 2-methylhept-2-en-6-ol, 1569-60-4; 3-phenylpropionic acid, 501-52-0; 2-hexyne, 764-35-2; 3-hexyne, 928-49-4; 1-propynylbenzene, 673-32-5; *N,N*-diethyl-2-butyn-1-amine, 73117-10-9; 2-butyne-1,4-diol, 110-65-6; ethynylbenzene, 536-74-3; *N,N*-diethyl-2-propyn-1-amine, 4079-68-9; 3-methyl-1-pentyn-3-ol, 77-75-8; 1-ethynylcyclohexyne, 931-49-7; *cis*-2-hexene, 7688-21-3; *cis*-3-hexene, 7642-09-3; *cis*-1-propenylbenzene, 766-90-5; *cis*-*N,N*-diethyl-2-penten-1-amine, 73117-11-0; *cis*-2-butene-1,4-diol, 6117-80-2; ethenylbenzene, 100-42-5; *N,N*-diethyl-2-propen-1-amine, 5666-17-1; 3-methyl-1-penten-3-ol, 918-85-4; 1-ethenylcyclohexene, 2622-21-1; 5-nonanone, 502-56-7; 1-phenylethanone, 98-86-2; cyclohexanone, 108-94-1; 2-methylcyclohexanone, 583-60-8; 3-methylcyclohexanone, 591-24-2; 4-methylcyclohexanone, 589-92-4; 2,6-dimethylcyclohexanone, 2816-57-1; 3,3,5,5-tetramethylcyclohexanone, 14376-79-5; 2-cyclohexylcyclohexanone, 90-42-6; 4-*tert*-butylcyclohexanone, 98-53-3; benzaldehyde, 100-52-7; heptanal, 111-71-7; 5-nonanol, 623-93-8; α-methylbenzenemethanol, 98-85-1; cyclohexanol, 108-93-0; *cis*-2-methylcyclohexanol, 7443-70-1; *trans*-2-methylcyclohexanol, 7443-52-9; *cis*-3-methylcyclohexanol, 5454-79-5; *trans*-3-methylcyclohexanol, 7443-55-2; *cis*-4-methylcyclohexanol, 7731-28-4; *trans*-4-methylcyclohexanol, 7731-29-5; *cis,cis*-2,6-dimethylcyclohexanol, 39170-84-8; *cis,trans*-2,6-dimethylcyclohexanol, 39170-83-7; *trans,trans*-2,6-dimethylcyclohexanol, 42846-29-7; *cis*-3,3,5-trimethylcyclohexanol, 933-48-2; *trans*-3,3,5-trimethylcyclohexanol, 767-54-4; 3,3,5,5-tetramethylcyclohexanol, 2650-40-0; *cis*-2-cyclohexylcyclohexanol, 51175-62-3; *trans*-2-cyclohexylcyclohexanol, 58879-21-3; *cis*-4-*tert*-butylcyclohexanol, 937-05-3; *trans*-4-*tert*-butylcyclohexanol, 21862-63-5; benzenemethanol, 100-51-6; 1-heptanol, 111-70-6; 5α-cholestan-3-one, 566-88-1; cholest-4-en-3-one, 601-57-0; cholest-5-en-3-one, 601-54-7; 5α-androstane-3,17-dione, 846-46-8; 3α,5α-cholestan-3-ol, 516-95-0; 3β,5α-cholestan-3-ol, 80-97-7; 5β-cholestan-3-one, 601-53-6; 3α,5α-3-hydroxyandrostan-17-one, 53-41-8; 3β,5α-3-hydroxyandrostan-17-one, 481-29-8; *tert*-amyl alcohol sodium salt, 14593-46-5; sodium hydride, 7646-69-7; nickel acetate, 373-02-4.

Facile Synthesis of Halo-Substituted Tetrahydroisoquinolines and Tetrahydro-2-benzazepines via *N*-Acetyl-1,2-dihydroisoquinolines

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A series of halo-substituted *N*-acetyl-1,2-dihydroisoquinolines (**3a–f**) has been prepared by a convenient and mild cyclization procedure. The synthetic utility of these compounds is demonstrated by their conversion to tetrahydroisoquinolines **5e** and **5f** and tetrahydro-2-benzazepines **10e** and **10f**, the latter via a cyclopropanation–ring expansion sequence.

1,2-Dihydroisoquinolines are interesting species due to both their chemical reactivity[1,2] and their potential as building blocks in the synthesis of alkaloids and medicinal agents. The most common method of generating these compounds involves the acid-catalyzed cyclization of (benzylamino)acetaldehyde dialkyl acetals, a procedure limited to those systems incorporating an election-rich aromatic ring.[1,3] Another route involves the reduction of isoquinolines[2] or their salts, which are usually obtained by a Pomeranz–Fritsch[4] or related reaction. Likewise, this approach is limited to electronically activated systems, and, furthermore, both methods involve the use of rather stringent reaction conditions.

We now report a mild and convenient method for the synthesis of a series of halo-substituted *N*-acetyl-1,2-dihydroisoquinolines (**3a–f**). We also describe the utilization of two of these (**3e,f**) in the preparation of the corresponding tetrahydroisoquinolines **5e,f**, as well as the 2-benzazepines **10e,f**, compounds that are only difficultly accessible by conventional procedures.

As illustrated in Scheme I, benzaldehydes **1** were converted to their Schiff bases with aminoacetaldehyde dimethyl acetal. Reductive acylation afforded **2** in good to excellent overall yields. Cyclization of **2** was effected by

(1) S. F. Dyke, *Adv. Heterocycl. Chem.*, 14, 279 (1972), and references therein.

(2) M. Natsume, S. Kumadaki, Y. Kanda, and K. Kiuchi, *Tetrahedron Lett.*, 2335 (1973).

(3) A. J. Birch, A. H. Jackson, and P. V. R. Shannon, *J. Chem. Soc., Perkin Trans. 1*, 2185 (1974).

(4) W. J. Gensler, *Org. React.*, 6, 191 (1951).

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