

Efficient Synthesis of Imines by a Modified Titanium Tetrachloride Procedure

Rolf Carlson,^{a,*} Ulf Larsson^a and Lars Hansson^b

^aDepartment of Organic Chemistry, Umeå University, S-901 87 Umeå, Sweden and ^bInstitute of Pharmacology, University of Gothenburg, S-413 90 Gothenburg, Sweden

Carlson, R., Larsson, U. and Hansson, L. Efficient Synthesis of Imines by a Modified Titanium Tetrachloride Procedure. – Acta Chem. Scand. 46: 1211–1214.

A general method for the synthesis of imines (azomethine compounds) is to react the corresponding aldehyde or ketone with a primary amine to form a carbinolamine which is dehydrated to yield the imine. Different techniques have been employed for the removal of water from the reaction mixture, some examples being azeotropic distillation using benzene or toluene as solvent,¹ running the reaction in the presence of molecular sieves or alumina to trap the water,² and using anhydrous salts which irreversibly bind the water.^{1,3} Analogous techniques can be used for the synthesis of enamines from carbonyl compounds and secondary amines.⁴ Methods which employ anhydrous titanium tetrachloride as a water scavenger have been described for the synthesis of both imines³ and enamines.⁵

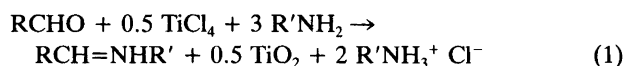
In previous papers from this laboratory⁶ it was reported that the original titanium tetrachloride procedure for enamine synthesis by White and Weingarten⁵ could be considerably improved by changing the order of introducing the reagents. In the original procedure, titanium tetrachloride was added to a mixture of the carbonyl compound and the amine in hydrocarbon solvent. The procedure required prolonged stirring and afforded moderate yields. In the modified procedure, the carbonyl compound was added to a preformed complex between the amine and titanium tetrachloride suspended in a hydrocarbon solvent. With this procedure, the reaction time could be considerably shortened (in many cases to only a few minutes) and in most cases afforded quantitative conversions.

In the present paper, we report that the modified titanium tetrachloride procedure can be extended to the synthesis of imines from carbonyl compounds and primary amines.

Methods and results

The stoichiometry of the reaction is shown in eqn. (1).

*To whom correspondence should be addressed.



For enamine synthesis, it was found that the amount of titanium tetrachloride and amine which should be used to obtain a maximum yield were highly dependent on the nature of the substrate.⁶ As this might also apply to imine synthesis, the experimental conditions for systems selected were adjusted by means of factorial experimental design, simplex technique or response surface technique to afford the maximum yield. In all cases studied this corresponded to a quantitative (98–100%) conversion. The experimental variables to be adjusted were determined by screening experiments using two-level fractional factorial designs. For details on these techniques, see Ref. 7. The following combinations of carbonyl substrates and amines were studied by these methods: cyclohexanone, 2-decalone, *p*-methoxybenzaldehyde with cyclohexylamine; cyclohexanone with *tert*-butylamine and benzylamine. The selection of test systems was based upon principal properties.⁷

In the optimization experiments, the yield of imine was determined by gas liquid chromatography (GLC) using the internal standard technique. Table 1 (entries 1–5) summarizes the optimum conditions thus determined. Representative response surface projections are shown in Fig. 1. Preparative runs under the same conditions afforded, after distillation isolated yields of the pure imine in the range 87–95%.

The reactions could conveniently be carried out at room temperature and afforded the maximum yield within 2 h. There was one exception, *viz.* the synthesis of *N*-cyclohexylidenebenzylamine for which the reaction was slow at room temperature but which afforded a quantitative conversion when it was carried out under reflux conditions, see Fig. 1(b).

The results show that in most cases an excess of titanium tetrachloride rather than a stoichiometric amount should be used and a fairly large excess of the amine. In general, a

Table 1. Summary of experimental conditions and yields obtained in the synthesis of imines.

Entry	Reactants		Optimum conditions		Yield (4)
	Substrate, C	Amine, A	Ratio TiCl ₄ /C	Ratio A/C	
1	Cyclohexanone	<i>t</i> -BuNH ₂	0.7	4.9	99 ^a
2	Cyclohexanone	Cyclohexylamine	0.8	6.4	96–100 ^a
3	Cyclohexanone ^b	PhCH ₂ NH ₂	1.2–1.4	6.0	95–98 ^a
4	2-Decalone	Cyclohexylamine	0.9	8.9	97 ^a
5	<i>p</i> -Methoxybenzaldehyde	Cyclohexylamine	0.6	3.6	100 ^a
6	2-Tetralone	(–)-1-Phenylethylamine	0.8	^c	82 ^d
7	2,6-Dimethylcyclohexanone	(±)-1-Phenylethylamine	1.0	^e	90 ^e

^aDetermined by GLC directly on the reaction mixture using an internal standard technique. ^bThe reaction was carried out under reflux in hexane. ^cThe amounts of amines were: 1.0 equiv. of 1-phenylethylamine and 6.0 equiv. of triethylamine. ^dIsolated yield of distilled product in preparative-scale synthesis. ^eThe reaction was carried out under reflux in isooctane. ^fThe amounts of amines were: 1.33 equiv. of 1-phenylethylamine and 7.6 equiv. of triethylamine.

six- to ten-fold excess of amine with respect to titanium tetrachloride should be used. This is acceptable as long as the amine is cheap and readily available but would be wasteful with complex or difficult-to-prepare amines. It occurred to us that one way of overcoming this inconvenience would be to use a tertiary amine as an auxiliary reagent to yield a reactive mixed amine–titanium tetrachloride complex. The results obtained using a stoichiometric amount or only a slight excess of 1-phenylethylamine as the primary amine and an excess of triethylamine in reactions with 2-tetralone and 2,6-dimethylcyclohexanone, respectively, are shown in Table 1 (Entries 6, 7).

The reasons for selecting these ketones as model substrates were the following. (a) Chiral imines from 2-tetralone derivatives are used for the synthesis of pharmacologically active compounds.⁸ If the yield could be improved, this would be of general interest to chemists in the field of medicinal chemistry. (b) The reaction of 2,6-dimethylcyclohexanone using a three-fold excess of 1-phenylethylamine has been reported to yield 76% of the corresponding imine by the original titanium tetrachloride procedure.⁹ This gives us an opportunity to compare results obtained by the original method with those obtained by the modified procedure presented in this paper. The imine from this ketone has been reported as a key intermediate in the syntheses of certain terpenoids.⁹

A method for the reductive amination of ketones in the presence of tertiary amines and using titanium tetrachloride and sodium cyanoborohydride as reagents appeared¹⁰ during the course of the present work.

Discussion

Complex formation between titanium tetrachloride and amines has been the subject of several studies.¹¹ Different complexes can be formed which are in dynamic equilibrium with each other. We suggest the following rationalization for the observed sensitivity of the reaction to variations in the amounts of amine and titanium tetrachloride.

The reaction between titanium tetrachloride, which is a Lewis acid, and amine base is rapid. The reactive constituent which interacts with the carbonyl compound is neither the free amine nor the free titanium tetrachloride: it is one of the complexes between titanium tetrachloride and the amine. As the complexes are in equilibrium, the concentration of the reactive complex is dependent on the initial relative proportions of the amine and titanium tetrachloride in the reaction mixture. The equilibrium constants for the complex formation will probably depend on the nature

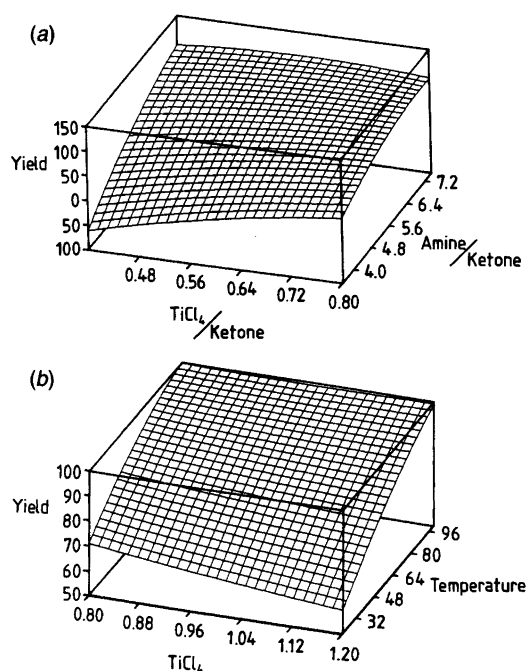


Fig. 1. (a) Projection of the response surface showing the variation in the yield of *N*-cyclohexylidene-*tert*-butylamine when the ratios of titanium tetrachloride/ketone and of cyclohexylamine/ketone were varied. (b) Projection of the response surface showing the variation in the yield of *N*-cyclohexylidenebenzylamine when the ratio of titanium tetrachloride/ketone and the reaction temperature (°C) were varied.

of the amine. With different amines, the initial proportions of amine to titanium tetrachloride should be adjusted to afford a sufficiently high concentration of the reactive complex. Even when this is fulfilled it might be necessary to use an excess of the reagents to obtain a conveniently rapid conversion of the substrate.

The modified method given in this paper affords improved yields compared with the original procedure. However, the detailed experimental conditions for quantitative conversions are, for the reasons discussed above, dependent on the nature of the amine and on the substrate to be transformed. Accordingly, it was necessary to adjust the reaction conditions and for this purpose multivariate methodology is essential. The danger of using standardized conditions for the exploration of synthetic reactions has been emphasized elsewhere.⁷

The use of a triethylamine as an auxiliary reagent in the formation of the titanium tetrachloride amine complex offers a means of carrying out efficient transformations with stoichiometric amounts of primary amines and this broadens the scope of the present method.

Experimental

General techniques. ¹H (80 MHz) and ¹³C NMR (20.25 MHz) were recorded using deuteriochloroform as the solvent. Mass spectra were obtained using electron impact (EI) ionization at 70 eV. Mass spectra are reported as follows: *m/z* (% relative abundance) [assignment]. GLC analyses were carried out using a 30 m 0.53 mm i.d. capillary column coated with SPB-20 or Supelcowax 10. Integrated peak areas were used for quantification. Boiling points in Kugelrohr distillations refer to the oven temperature.

Chemicals. Starting materials, reagents and solvents were commercial *puriss.* or *p.a.* grade with the exception of 2-tetralone which was prepared from its bisulfite adduct immediately before use. 2-Tetralone was synthesized via Birch reduction of 2-ethoxynaphthalene according to Ref. 12.

General procedure for the optimization experiments. The reactions were carried out in an oven-dried 100 ml three-necked flask equipped with a reflux condenser, Hershberg stirrer and a dropping funnel. The flask was purged with dry nitrogen prior to introduction of the reagents and a nitrogen atmosphere was maintained during the course of the reaction. The calculated amount of amine (experimental variable), the amount of solvent (hexane) (experimental variable), and an accurately weighed amount of icosane (internal standard) were introduced and the mixture was cooled in an ice-bath. The calculated amount of titanium tetrachloride (experimental variable) dissolved in 5–10 ml of hexane was added dropwise with efficient stirring. After 5 min the ice-bath was removed and 10 mmol of the substrate were introduced in one portion. Liquid substrates

were added as such, solid substrates were dissolved in a small volume of hexane. The reaction was allowed to proceed at the temperature given (experimental variable). The temperature was controlled by means of an oil-bath. The reaction was monitored by GLC and was assumed to be complete when there was no further increase in yield. For reactions carried out at room temperature, a reaction time of 2 h was sufficient. For reactions carried out under reflux, the maximum yield was attained within 0.5 h.

Preparative runs under the conditions given in entries 1–5, Table 1 were performed analogously but without the addition of an internal standard. After distillation, isolated yields of pure (>98 %) imine were in the range 87–95 % for all compounds.

Physical properties if the imines in entries 1–5, Table 1. The *Z/E* isomers of the imines were not assigned in the NMR spectra. *N*-Cyclohexylidene-*tert*-butylamine, b.p. 66°C/6–7 mmHg (lit.¹³ 83–85°C/20 mmHg), *N*-cyclohexylidene-cyclohexylamine, b.p. 114°C/7 mmHg (lit.¹⁴ 121–123.4°C/10 mmHg), *N*-cyclohexylidenebenzylamine, b.p. 94–97°C/5 mmHg (lit.¹⁵ 125–128°C/1 mmHg) are known compounds and their spectral properties are not given here.

N-(*p*-Methoxybenzylidene)cyclohexylamine. B.p. 113–114°C/0.05 mmHg, m.p. 33°C. ¹H NMR: 1.51–1.62 (m, 10 H), 3.15 (m, 1 H), 3.77 (s, 3 H), 6.87 (m, 2 H), 7.65 (m, 2 H), 8.21 (s, 1 H). ¹³C NMR: 24.75, 25.61, 34.40, 55.10, 69.62, 113.76, 129.40, 129.61, 157.56, 161.28. IR: (KBr) 1647, 883 cm⁻¹. MS: 217 (32) [*M*⁺], 216 (36), 189 (41), 174 (42), 134 (100), 91 (37), 77 (45), 55 (45), 41 (71).

N-(Decahydro-2-naphthylidene)cyclohexylamine. B.p. 110–117°C/0.1 mmHg. ¹H NMR: 1.16–1.70 (m, 22 H), 2.01–2.61 (m, 5 H). ¹³C NMR: (mixture of *Z* and *E* isomers) 11.77, 22.66, 23.09, 24.12, 24.48, 15.25, 25.77, 26.52, 28.30, 28.80, 29.23, 32.93, 34.28, 34.47, 35.95, 38.28, 38.55, 40.02, 43.51, 43.92, 44.35, 47.25, 58.07, 58.30, 170.00. IR: (neat film) 1650 cm⁻¹. MS: spectra of both isomers by GLC–MS *Isomer 1*: 233 (34) [*M*⁺], 190 (41), 152 (46), 136 (32), 98 (16), 67 (39), 55 (93), 41 (100); *Isomer 2*: 233 (21) [*M*⁺], 190 (50), 152 (16), 136 (16), 67 (35), 55 (83), 41 (100).

Synthesis of the imine from 2-tetralone and (–)-1-phenylethylamine. All solvents were dried and deoxygenated before use. Deoxygenation was carried out by passing a rapid stream of dry nitrogen through the dry solvent for ca. 15 min. Without this precaution highly coloured products were obtained.

An oven-dried 500 ml three-necked flask was equipped with a dropping funnel, a Hershberg stirrer, and a reflux condenser. The flask was purged with nitrogen prior to introduction of the reagents, and a positive pressure of nitrogen was maintained in the apparatus throughout the whole operation. The flask was charged with 6.06 g (50 mmol) of (–)-1-phenylethylamine, 30.36 g (300 mmol) of triethylamine and 100 ml of hexane. The mixture was cooled to ca. 5°C by means of an ice-bath and a solution of

4.39 ml (0.40 mmol) of titanium tetrachloride in 50 ml of hexane was added dropwise over a period of ca. 10 min. The precipitated titanium tetrachloride-amine complexes were homogenized and suspended by vigorous stirring for a few minutes prior to introduction of the ketone. The vigorous stirring of the suspended complexes was maintained and a solution of 7.31 g (50 mmol) of 2-tetralone [3,4-dihydro-2(1*H*)-naphthalenone] in a 50 ml of diethyl ether-hexane (1:1) was added in one batch. The ice-bath was removed and the reaction was allowed to proceed at reflux for 2 h. The mixture was cooled to room temperature and 200 ml of diethyl ether were added to precipitate the titanium complexes. Under a protective nitrogen atmosphere, the reaction mixture was filtered through a sintered glass filter (porosity No. 3). The solid material in the reaction flask and on the filter was rinsed with four 50 ml portions of diethyl ether. The solvent was removed by evaporation under reduced pressure and the residual crude product was distilled in a Kugelrohr apparatus to afford 10.2 g (82 %) of pure (>98 %, GLC) (-)-*N*-(1-phenylethyl)-2-amino-3,4-dihydronaphthalene (enamine tautomer). It is interesting to note that the free imine could not be detected in the NMR spectra of the final product derived from 2-tetralone; only the enamine tautomer was present.

The product is extremely oxygen-sensitive. With normal precautions, such as storage in the dark in the freezer under an atmosphere of dry nitrogen, the product turns yellow within 48 h. Rigorous exclusion of oxygen is therefore necessary if the product is to be stored for longer periods.

Physical data: b.p. 180–190 °C/0.5 mmHg. $[\alpha]_D^{25} = -87^\circ$ (c 68, chloroform). ¹H NMR: 1.41 (d, 3 H), 2.22 (m, 2 H), 2.74 (m, 2 H), 3.49 (br s, 1 H), 4.45 (m, 1 H), 5.03 (s, 1 H), 7.3–6.6 (m, 9 H). ¹³C NMR: 24.14, 28.45, 29.20, 52.70, 94.50, 122.34, 123.46, 126.42, 126.67, 126.83, 128.52, 130.79, 137.39, 144.55, 144.75. MS: 249 (79) [*M*⁺], 145 (100), 144 (30), 105 (93), 79 (17), 77 (21).

Synthesis of *N*-(2,6-dimethylcyclohexylidene)-1-phenylethylamine. The equipment and experimental procedure were as described above. The proportions of reagents were, however, different and isooctane was used as solvent throughout. The flask was charged with 7.30 g (61 mmol) of (±)-1-phenylethylamine, 35.42 g (350 mmol) of triethylamine, and 100 ml of isooctane. To the cooled, stirred, mixture was added dropwise a solution of 5.0 ml (46 mmol) of titanium tetrachloride in 50 ml of isooctane, followed by the rapid introduction of 5.80 g (46 mmol) of 2,6-dimethylcyclohexanone in ca. 10 ml of solvent. Work-up as above and Kugelrohr distillation afforded 9.52 g (90 %) of pure (>98 %, GLC) imine. The product was a (1:2) mixture of *cis* and *trans* isomers.

Physical properties: b.p. 125–130 °C/0.5 mmHg. ¹H NMR: 0.9–1.9 (m, 15 H), 2.5 (m), 3.10 (m), 4.74 (dq,

1 H), 7.2–7.4 (m, 5 H). ¹³C NMR: 17.27, 17.38, 17.47, 17.87, 20.51, 20.64, 25.99, 31.02, 31.18, 33.14, 33.71, 36.58, 36.67, 36.93, 37.02, 56.91, 57.20, 126.08, 126.16, 126.43, 126.70, 128.11, 128.28, 147.42, 175.22, 175.70. MS: The stereoisomers showed identical mass spectra: 229 (15) [*M*⁺], 214 (5), 138 (4), 106 (13), 105 (100), 77 (11), 41 (8). IR: (neat film) 1655 cm⁻¹.

Acknowledgements. We thank Mr. Asgedom Negasi for some of the experiments in the optimization of the synthesis of *N*-cyclohexylidenebenzylamine. Financial support from the Swedish Natural Science Research Council and from the National Swedish Board for Technical Development is gratefully acknowledged.

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Received May 7, 1992.