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Ketoform reaction. Synthesis of hindered imines from 2,6-dialkylanilines and ketones

John T. Lai*

Noveon, Inc., 9911 Brecksville Rd, Brecksville, OH 44141, USA

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Abstract—Hindered imines are synthesized from 2,6-dialkylanilines, ketones, chloroform and sodium hydroxide in a phase-transfer catalyzed reaction. © 2002 Elsevier Science Ltd. All rights reserved.

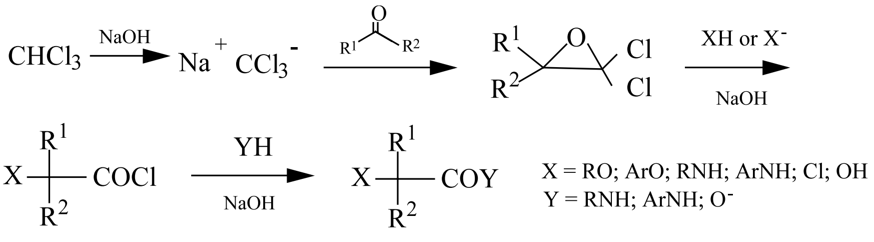
Hindered imines derived from 2,6-di-alkylanilines and ketones are difficult to prepare. They have been isolated as silver iodide salts,[1] and recently-reported synthetic methods employ harsh conditions that include the use of strong Lewis acid catalyst,[2] or strong dehydrating agent.[3] In this report, we describe a new method employing mild, basic conditions where the imines are easily isolated in high yields. It is one of several applications from our studies of the ketoform reaction.[4]

In the ketoform reaction, a ketone, chloroform and sodium hydroxide provide a reactive 1,1-dialkyl-2,2-dichlorooxirane intermediate that can be selectively opened to an acyl chloride with nucleophiles. Further condensation with the same or different nucleophile gives a stable product (Scheme 1).

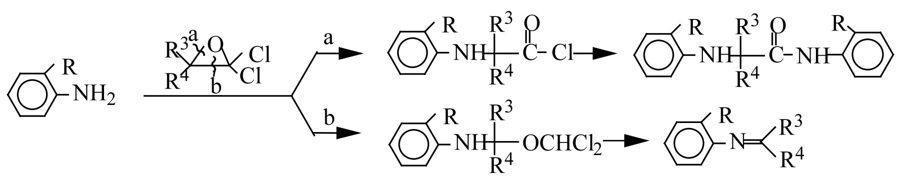
Usually, nucleophiles break the dialkyl carbon–oxygen bond in the oxirane (Scheme 2, path a). However, 2-alkylanilines are an exception.[5] They preferentially break the carbon–carbon bond, leading to the imine (Scheme 2, path b).

We now report that 2,6-dialkylanilines break only the carbon–carbon bond of the oxirane in the ketoform reaction, and hindered imines are the exclusive products (Scheme 3).

The process involves the mixing of a ketone (0.2 mol), chloroform (0.15 mol) and 2,6-dialkylaniline (0.1 mol), the phase-transfer catalyst Aliquot® 336 (0.004 mol) and 100 ml toluene at 10°C under a nitrogen atmosphere. Sodium hydroxide (50%, 0.5 mol) is then added



Scheme 1.



Scheme 2.

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* Corresponding author.

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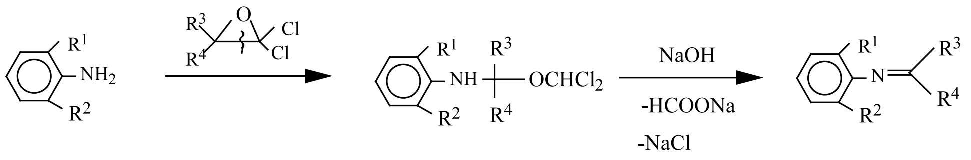
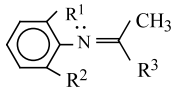


Scheme 3.

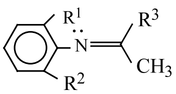
dropwise to keep the temperature below 20°C. After the addition, the reaction is allowed to continue overnight at 15°C. The reaction mixture is then filtered, and the solid removed is rinsed with toluene. The filtrate is washed with 50 ml water, dried over magnesium sulfate and concentrated to yield the crude product which is mainly imine, but can include some unreacted aniline and ketone. Pure compound can be obtained by distillation through a Vigraux column.

Table 1 shows examples of selected hindered imines made in this manner.

When R^3 and R^4 are different, the geometric *syn* and *anti* isomers[6] exhibit a ratio of about 15:85 from their ^1H NMR spectra, with little influence from the size of the R groups.

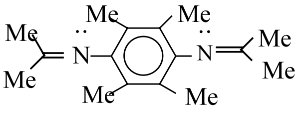


syn

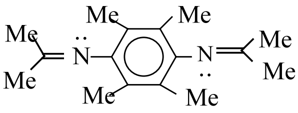


anti

In diimine **1i**, the *syn* and *anti isomers* are present in a 38:62 ratio based on ^1H NMR.



syn



anti

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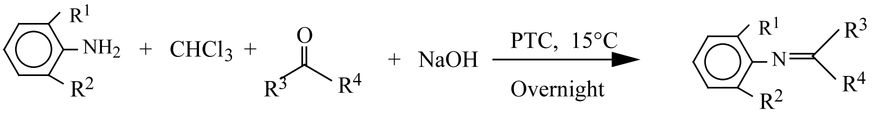
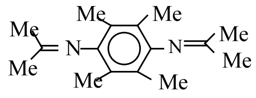
Table 1.



	R^1	R^2	R^3	R^4	Bp (°C/torr)	^1H NMR[a] (δ, $CDCl_3$)	Yield[b] (%)
1a	Me	Me	Me	Me	85–8/5	1.61 (s, 3H), 1.99 (s, 6H), 2.21 (s, 3H), 6.8–7.3 (m, 3H)	>95 (77)
1b	Me	Me	Me	Et	84–7/1	0.98 and 1.25 (2t, 18/82 ratio, 3H), 1.61 and 2.20 (2s, 82/18, 3H) 1.98 (s, 6H), 2.16 and 2.47 (2q, 18/82, 2H), 6.8–7.1 (m, 3H)	91 (64)
1c	Me	Me	-$(CH_2)_5$-		118–23/7.5	1.5–2.0 (m, 8H), 2.00 (s, 6H), 2.54 (t, 2H), 6.8–7.0 (m, 3H)	>95 (79)
1d	Me	Me	Me	*i*-Bu	–	0.81 and 1.05 (2d, 13/87, 6H), 1.60 and 2.20 (2s, 13/87, 3H), 2.00 (s, 6H), 1.9–2.4 (m, 3H), 6.8–7.0 (m, 3H)	62
1d[c]	Me	Me	Me	*i*-Bu	110–2/1		73 (43)
1e	Me	Me	Me	*n*-Hex	128–31/0.9	0.83 and 0.91 (2t, 15/85, 3H), 1.1–2.3 (m, 8H), 1.62 and 2.21 (2s, 85/15, 3H), 1.91 and 2.45 (2t, 15/85, 2H), 1.99 (s, 6H), 6.8–7.0 (m, 3H)	43 (20)
1f	Me	*i*-Pr	-$(CH_2)_5$-		137–43/1	1.12 (d, 3H), 1.66 (d, 3H), 1.5–2.0 (m, 8H), 2.55 (t, 3H), 2.55 (hept, 1H), 6.9–7.1 (m, 3H)	>95 (81)
1g	Et	Et	Me	Et	120–5/6	1.00 and 1.26 (2t, 15/85, 3H), 1.13 (t, 6H), 1.64 and 2.22 (2s, 85/15, 3H), 2.00 and 2.48 (2q, 15/85, 2H), 2.2–2.3 (m, 4H), 6.9–7.1 (m, 3H)	83 (67)
1h	Et	Et	-$(CH_2)_5$-		140–5/1	1.14 (t, 6H), 1.5–2.6 (m, 14H), 6.9–7.1 (m, 3H)	>95 (76)
1i					(155–60)[d]	1.58–1.60 (2s, 38/62, 6H), 1.89 (s, 12H), 2.23 (s, 6H)	95 (40)

[a] Bruker WH-200 spectrometer.

[b] Yield as measured by GC, with the isolated yield in parenthesis. The large differences between the two yields in **1b**, **1d** and **1e** are due to the close proximity between the boiling points of the aniline and the imine, thus it is difficult separation. Correct mass ion from chemical ionization mass spec by a Finnigan MAT spectrometer: ±0.0009; infrared spectra of neat or KBr pellet all show peaks at 1665–1775 cm^{-1}.

[c] 0.4 mol of MIBK is used instead of 0.2 mol of ketone used for the rest of the syntheses.

[d] Melting point, after recrystallization from hexanes.

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