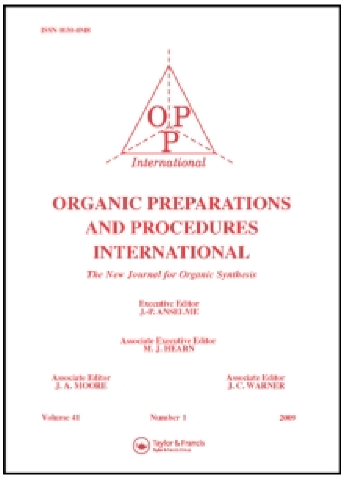

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A COMPARISON OF IMINE FORMING METHODOLOGIES

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A COMPARISON OF IMINE FORMING METHODOLOGIES

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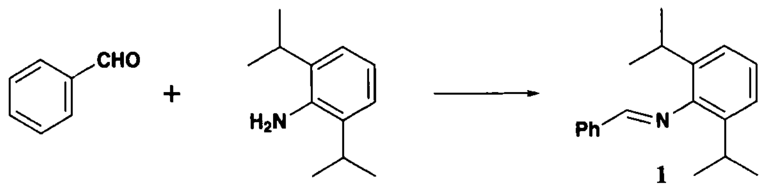
The significance of imines both in synthesis and biological chemistry has led to the development of a large number of methods for the formation of carbon-nitrogen double bonds.[1] A majority of these procedures involve the condensation of a primary amine with a carbonyl compound under conditions which remove water either chemically or physically. While most reactions proceed in good yield, those involving acid-sensitive carbonyl compounds or weakly nucleophilic amines can be troublesome, sometimes leading to decomposed starting materials and little or none of the desired imine. Reactions in which either (or both) of the two reactants is sterically hindered can also be sluggish and result in poor or no yield of products. Recently we[2] and others[3] have found that orthoesters of both organic and inorganic acids are useful for facilitating imine formation, especially in these difficult cases. This methodology has also been used for the synthesis of enamines from amines and carbonyl compounds.[4,5]

Due to the significant synthetic utility of these imine-forming reactions, we sought to determine which reagents were the most effective for given classes of substrates, and herein report the results of those studies. Three compounds which had previously been shown to be effective condensation agents for imine formation were investigated: trimethyl orthoformate (TMOF),[3] tetraethyl orthosilicate (TEOS),[2] and titanium (IV) isopropoxide (TIP).[6] One of the more commonly used methods of imine formation, heating a solution of the reactants at reflux in the presence of a Dean-Stark trap, was also investigated for the sake of comparison. In addition, the necessity for acid catalysis was investigated for all four of these methods. Orthoformates were chosen in preference over the more reactive dehydration agent/Lewis acid $TiCl_4$[7] since they do not produce acidic by-products and thus do not necessitate the use of excess amounts of the amine component.

Six compounds, chosen as representative examples of various types of imines, were prepared (*Eqs 1-6*). *Eqs 1* and *2* depict reaction of an unhindered aldehyde with a very hindered amine and a very non-nucleophilic amine,[8] respectively, while the reactions shown in *Eqs 3* and *4* were conducted to explore the reaction of an acid-sensitive aldehyde with the same compounds. *Eq. 5* illustrates an example of a reaction between a hindered ketone and a weakly nucleophilic amine, while *Eq. 6* represents the reaction of a hindered ketone (which is also stabilized by conjugation) with a very hindered amine. The results of these investigations are summarized in Tables 1 and 2.

In the condensation of hindered amines with aldehydes (*Eqs 1* and *3*) all four methods proved effective. Standard Dean-Stark methodology is perhaps the most straightforward method for preparing such imines, though it does, of course, require heating either a benzene or toluene solution of the reactants to reflux, while the orthoester-facilitated condensations can be conducted at room temperature (see Entries 5, 8, 9, 24 and 25 in Table 1). Of the two orthoesters investigated at room temperature, the TMOF method reported by Look, *et al.*[3] offers the advantage of easier removal of by-products. In some instances, however, conversion of the amine to the corresponding imidate was observed when TMOF was used. Imidate formation increased if the reaction was heated above room temperature.



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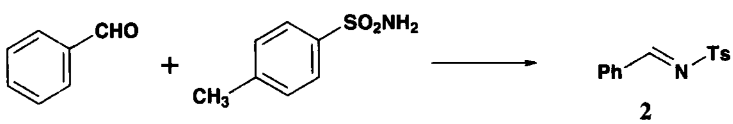

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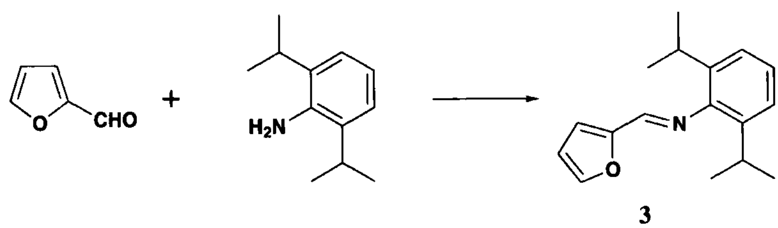

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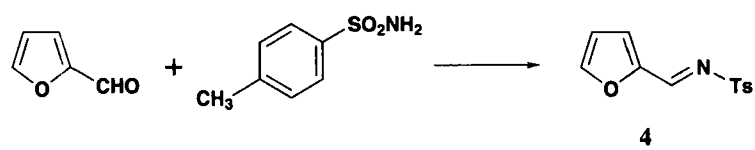

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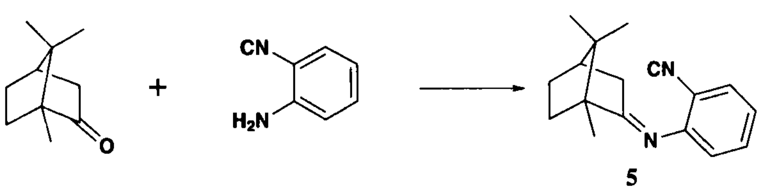

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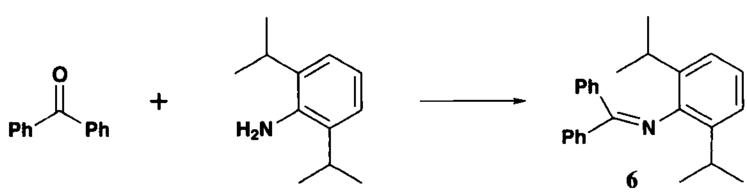

(6)

TABLE 1. Formation of Aldimines

Entry	Rxn.	Rxn. Cond.[a]	Dehydr. Agent	Catalyst	Yield (%)[b] (Purity)[c]
1	1	A	Dean-Stark	None	86 (75)
2	1	A	Dean-Stark	H_2SO_4	74 (100)
3	1	A	TEOS	None	99 (80)
4	1	A	TEOS	H_2SO_4	100 (80)
5	1	B	TEOS	None	90 (70)
6	1	A	TIP	None	49 (90)
7	1	A	TIP	H_2SO_4	62 (95)
8	1	B	TMOF	None	83 (75)
9	1	B	TMOF	H_2SO_4	98 (75)
10	2	C	Dean-Stark	None	0[d]
11	2	C	Dean-Stark	H_2SO_4	110 (50)/54 (90)[e]
12	2	C	TEOS	None	148 (70)/47 (100)[e]
13	2	C	TEOS	H_2SO_4	164 (40)/0[e,f]
14	2	C	TIP	None	158 (75)/77 (100)[e]
15	2	C	TIP	H_2SO_4	191 (50)/85 (90)[e]
16	2	C	TMOF	None	110 (60)/53 (90)[e]
17	2	C	TMOF	H_2SO_4	113 (30)/78 (30)[e]
18	3	A	Dean-Stark	None	87 (75)
19	3	A	Dean-Stark	H_2SO_4	92 (100)
20	3	A	TEOS	None	124 (60)
21	3	A	TEOS	H_2SO_4	113 (60)
22	3	A	TIP	None	69 (100)
23	3	A	TIP	H_2SO_4	66 (95)
24	3	B	TMOF	None	83 (60)
25	3	B	TMOF	H_2SO_4	96 (85)
26	4	C	Dean-Stark	None	0[d]
27	4	C	Dean-Stark	H_2SO_4	134 (20)/0[e,f]
28	4	C	TEOS	None	168 (40)/58 (100)[e]
29	4	C	TEOS	H_2SO_4	0[e,f]
30	4	C	TIP	None	185 (40)/64 (50)[e]
31	4	C	TIP	H_2SO_4	192 (40)/0[e,f]
32	4	C	TMOF	None	123 (20)/0[e,f]
33	4	C	TMOF	H_2SO_4	0[f]

a) Reaction conditions: (A) 150°, 20 h; (B) 25°, 16 h; (C) 150°, 6 h. b) Based on weight of crude product. c) Estimated by NMR and/or GC analysis. d) Only starting materials obtained. e) After recrystallization. f) Decomposed.

TABLE 2. Formation of Ketimines

Entry	Rxn.	Rxn. Cond.[a]	Dehydr. Agent	Catalyst	Crude Yield(%)[b]	Approx. Purity(%)[c]
1	5	A	Dean-Stark	None	0[d]	
2	5	A	Dean-Stark	H_2SO_4	86	30
3	5	A	TEOS	None	100	70
4	5	A	TEOS	H_2SO_4	108	70
5	5	A	TIP	None	74	65
6	5	A	TIP	H_2SO_4	68	20
7	5	B	TMOF	None	0[d]	
8	5	B	TMOF	H_2SO_4	0[e]	
9	6	C	Dean-Stark	H_2SO_4	0[d]	
10	6	C	TEOS	None	0[d]	
11	6	C	TEOS	H_2SO_4	59	95
12	6	C	TIP	None	0[f]	
13	6	C	TIP	H_2SO_4	traces[g]	
14	6	B	TMOF	None	0[e]	

a) Reaction conditions: (A) 150°, 20 h; (B) 25°, 16 h; (C) 150°, 40 h. b) Based on weight of crude product. c) Estimated by NMR and/or GC analysis. d) Only starting materials obtained. e) Only starting ketone and imidate obtained. f) Starting amine and benzhydrol obtained. g) Mostly starting amine and benzhydrol obtained.

Reactions of aldehydes with compounds possessing very weakly nucleophilic NH_2 groups, such as *p*-toluenesulfonamide (*Eqs 2* and *4*), are more difficult. Here use of orthoesters was generally more successful than a Dean-Stark trap, but only moderately so, since purification of the products became more difficult. Once again, the product prepared using trimethyl orthoformate was found to be contaminated with imidate, while silicon and titanium by-products were significant contaminants in the TEOS and TIP reactions, respectively. While treatment with ethanolic KOH is an effective means of removing these by-products when simple *N*-aryl imines are prepared,[2a,6] such conditions would hydrolyze tosylimines **2** and **4**, and thus purification by recrystallization from ethyl acetate/pentane became necessary.

The sensitivity of 2-furaldehyde to acids played a significant role only in the reaction with *p*-toluenesulfonamide (*Eq. 4*). For this reaction, a pure product was only obtained from those reactions conducted in the absence of sulfuric acid. On the other hand, comparable yields were obtained in the condensation with 2,6-diisopropylaniline (*Eq. 3*) for both the catalyzed and non-catalyzed reactions.

For condensation of hindered ketones with weakly nucleophilic amines, (*Eq. 5*), the Dean-Stark method was not as effective as the use of tetraethyl orthosilicate (compare Entries 1 and 2 with Entries 3 and 4 in Table 2), and was completely ineffective for the preparation of imine **6**. In fact, of the reagents tested, only tetraethyl orthosilicate provided **6** in significant amounts. Use of a catalytic amount of sulfuric acid appeared to be necessary for the success of this reaction, which is in contrast to other imine-forming reactions in this study, where catalytic sulfuric acid did not improve TEOS-promoted reactions significantly, and in some cases was found to lower the yield. Titanium(IV) isopropoxide was moderately effective in the formation of **5**, but not **6**, reducing the benzophenone to benzhydrol instead, a reaction noted previously.[9]

With respect to the formation of imines of aldehydes, it appears that use of orthoesters is only advantageous over standard Dean-Stark methodology when the substrate cannot tolerate being heated at reflux. While all of the orthoesters are effective at room temperature, trimethyl orthoformate is perhaps the best of the three tested. It offers a combination of high product yield and ease of purification, though in some instances imidate formation was found to compete with imine synthesis. Other dehydration agents which are effective at room temperature, such as molecular sieves,[10] were not evaluated in this study. For the preparation of imines derived from weakly nucleophilic amines, tetraethyl orthosilicate proved to be the most effective condensation agent. In most cases, yields of imines were found to be higher with TEOS than with titanium(IV) isopropoxide, and the silicon-containing by-products (silicon dioxide and siloxane oligomers) were more easily removed from the product mixture than were the titanium dioxide and other titanium-containing compounds that resulted from the use of TIP. Imines derived from a hindered ketone with a hindered amine (*Eq. 6*) could only be obtained with TEOS as the condensation agent.

With the exception of the case noted earlier (Entry 11, Table 2), acid catalysis of orthoester-mediated reactions did not generally offer any significant advantage over non-catalyzed reactions run under neutral conditions. Acid catalysis did generally improve the yields, however, for reactions run using a Dean-Stark trap, and in some cases (*Eqs 2, 4* and *5*) was found to be essential.

EXPERIMENTAL SECTION

Reactions were all conducted under a nitrogen atmosphere for the times and at the temperatures specified in Tables 1 and 2. Equimolar amounts of amine and carbonyl compound were used in all cases. Reactions conducted with a Dean-Stark trap utilized toluene as a solvent, while the orthoesters were used as solvent in the other reactions. For reactions conducted in TEOS and TIP, approximately 1.5 equivalents of condensation agent (relative to the amount of amine) were used, while 2 mL of TMOF (approximately 20 equivalents) were used for every millimole of amine. Work-up consisted of dilution of the product mixture with ether, and washing this ether solution twice with distilled water then once with saturated NaCl. The ether layer was then dried ($MgSO_4$) and the solvent removed under reduced pressure. For those reactions in which H_2SO_4 was used, the first aqueous wash was replaced with 1M NaOH. The silicon- and titanium-containing impurities from reactions conducted with TEOS or TIP could be removed in the following manner: The crude product was dissolved in 95% ethanol and stirred for 15 min. with 5 mL of 1M KOH in ethanol. The precipitate which formed was removed by filtration and washed with ether. The filtrate was washed twice with water and once with saturated NaCl, then dried ($MgSO_4$) and the solvent removed under reduced pressure. ^{1}H and ^{13}C NMR spectra were obtained in $CDCl_3$ on a Varian Gemini 200 instrument operating at 200 and 50 MHz, respectively. TMS was used as an internal standard for ^{1}H spectra, and $CDCl_3$ was used for ^{13}C spectra. Compounds **1**,[11] **2**,[2b] **3**,[12] **4**,[2b] **5**[2a] and **6**[13] have all been reported previously. These compounds were identified by comparison of their spectra with those described in the literature.

***N*-Phenylmethylene-2,6-diisopropylaniline (1)**.- ^{1}H NMR: δ 8.21 (s, 1H), 7.8-8.0 (m, 2H), 7.4-7.5 (m, 3H) 7.1-7.2 (m, 3H), 3.00 (sept, *J* = 6.9 Hz, 2H), 1.18 (d, *J* = 6.9 Hz, 12H).

***N*-Phenylmethylene-*p*-toluenesulfonamide (2)**.- ^{1}H NMR: δ 9.03 (s, 1H), 7.8-8.0 (m, 3H), 7.2-7.7 (m, 6H), 2.43 (s, 3H).

***N*-(2-Furanylmethylene)-2,6-diisopropylaniline (3)**.- ^{1}H NMR: δ 7.98 (s, 1H), 7.57 (br s, 1H), 7.0-7.2 (m, 3H), 6.91 (d, *J* = 3.4 Hz, 1H), 6.5-6.6 (m, 1H), 3.01 (sept, *J* = 6.8 Hz, 2H), 1.16 (d, *J* = 6.8 Hz, 12H)

***N*-(2-Furanylmethylene)-*p*-toluenesulfonamide (4)**.- ^{1}H NMR: δ 8.81 (s, 1H), 7.87 (d, *J* = 8.3 Hz, 2H) 7.74 (d, *J* = 1.5 Hz, 1H)7.3-7.4 (m, 3H), 6.6-6.7 (m, 1H), 2.42 (s, 3H).

***N*-(Bornan-2-ylidene)-2-cyanoaniline (5)**.- ^{1}H NMR: δ 7.4-7.6 (m, 2H) 7.09 (dd *J* = 6.5 Hz, 8.1 Hz, 1H), 6.82 (d *J* = 8.1 Hz, 1H), 2.1-2.3 (m, 1H), 1.6-2.0 (m, 5H), 1.2-1.4 (m, 1H), 1.12 (s, 3H), 0.99 (s, 3H), 0.92 (s, 3H).

***N*-Diphenylmethylene-2,6-diisopropylaniline (6)**.- ^{1}H NMR: δ 7.79 (d, *J* = 6.5 Hz, 2H), 7.3-7.5 (m, 3H), 6.9-7.3 (m, 8H), 2.87 (sept, *J* = 6.8 Hz, 2H), 1.13 (d, *J* = 6.6 Hz, 6H), 0.93 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR: δ 22.4, 24.5, 28.9, 123.1, 123.7, 128.1, 128.4, 128.6, 129.4, 129.6, 129.7, 129.9, 130.8, 136.2, 147.0, 166.2.

REFERENCES

1. a) S. Patai, *"The Chemistry of the Carbon-Nitrogen Double Bond"* Wiley Interscience, New York, NY, 1970; b) G. M. Robertson, in "*Comprehensive Organic Functional Group Transformations*," A. R. Katritzky, O. Meth-Cohn and C. W. Rees, Eds., Vol. 3, p. 403, Elsevier, Tarrytown, NY, 1995.

2. a) B. E. Love and J. Ren, *J. Org. Chem.*, **58**, 5556 (1993); b) B. E. Love, P. S. Raje and T. C. Williams, II, *Synlett*, 493 (**1994**).

3. G. C. Look, M. M. Murphy, D. A. Campbell and M. A. Gallop, *Tetrahedron Lett.*, **36**, 2937 (1995).

4. S. I. Kirin, V. Vinkovic and V. Sunjic, *Chirality*, **7**, 115 (1995).

5. For an example of the successful use of tetraethyl orthosilicate as a condensation agent when other traditional methods failed, see: V. Vinkovic, and V. Sunjic, *Tetrahedron*, **53**, 689 (1997).

6. B. E. Love, Unpublished results.

7. R. Carlson, U. Larsson and L. Hansson, *Acta Chem. Scand.*, **46**, 1211 (1992).

8. Although it is understood that $TsNH_2$ is classified as a sulfonamide, not an amine, it nevertheless serves as an example of a very non-nucleophilic NH_2 group.

9. N. M. Khan, V. Arumugam and S. Balasubramanian, *Tetrahedron Lett.*, **37**, 4819 (1996).

10. K. Taguchi and F. H. Westheimer, *J. Org. Chem.*, **36**, 1570 (1971).

11. G. K. Cantrell and T. Y. Meyer, *Chem. Commun.*, 1551 (**1997**).

12. PCT Int. Appl. WO 97 02,298; *Chem Abstr.*, **126**, 199931c (1997).

13. Y. Makioka, A. Saiki, K. Takaki, Y. Taniguchi, T. Kitamura and Y. Fujiwara, *Chemistry Lett.*, 27 (**1997**).

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