

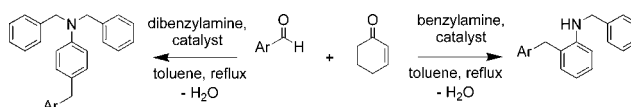
# Preparation of 2- and 4-Arylmethyl *N*-Substituted and *N,N*-Disubstituted Anilines via a “Green”, Multicomponent Reaction

Anthony E. Rosamilia, Janet L. Scott, and Christopher R. Strauss\*

ARC Special Research Centre for Green Chemistry, Monash University,  
Clayton, Victoria 3800, Australia  
chris.strauss@sci.monash.edu.au

Received January 28, 2005

## ABSTRACT



A new, green, regioselective, one-step, multicomponent reaction of an aldehyde possessing a nonenolizable carbonyl function, cyclohex-2-enone (or a derivative thereof), and primary or secondary amines afforded 2-*N*-substituted arylmethyl anilines or 4-*N,N*-disubstituted arylmethyl anilines, respectively. Yields and regioselectivities were good. Evidence for a pathway involving imine and iminium intermediates is presented along with examples demonstrating amenability of the process to combinatorial chemistry.

Aniline derivatives (**4** and **5**, see Scheme 1) possessing arylmethyl substituents at the 2 or 4-position are employed as antioxidants in lubricants<sup>1</sup> and as synthetic precursors of heterocyclic compounds<sup>2</sup> or of 4,4-diphenylmethane diisocyanate,<sup>3</sup> while others have shown a diverse array of biological activities with clinical potential in the treatment of bone diseases, cancer, and ulcers.<sup>4</sup>

Despite this broad range of applications, surprisingly few members of the family have been reported. Coupling reactions between substituted anilines and formaldehyde (or an equivalent) are commonly employed, but they usually afford symmetrical products.<sup>5</sup> Other published routes to **4** and **5** require several steps and have variable yields.<sup>6</sup> All of these approaches offer limited scope for structural diversity.

Our recent research has included reactions of nonenolizable aldehydes and ketones to afford green processes and products.<sup>7</sup> We now report a new one-step multicomponent reaction for the preparation of *N*-monosubstituted or *N,N*-disubstituted aniline derivatives (**4** and **5**), which offers great diversity and satisfies many of the principles of Green Chemistry.<sup>8</sup>

Three different classes of reactants are employed: an aldehyde **1** without an enolizable carbonyl function, cyclohex-2-enone or a derivative thereof **2**, and an amine **3**, which may be primary or secondary (see Scheme 1 and Table 1). The examples of **1–3** in Scheme 1 are not limiting. In the simplest manifestation, condensation of one molecule from each of the three classes affords the substituted anilino product plus two molecules of water. So far, reactions (Table 1) have been carried out preferably in refluxing toluene with a Dean–Stark apparatus employed for water removal in situ.

(1) Roberts, J. T. U.S. Patent 4,411,805, 1983.

(2) (a) Wardrop, A. W. H.; Sainsbury, G. L.; Harrison, J. M.; Inch, T. D. *J. Chem. Soc., Perkin Trans. 1* **1976**, 12, 1279. (b) Moffett, R. B. *J. Heterocycl. Chem.* **1980**, 17, 341. (c) Nifant'ev, E. E.; Zavalishina, A. I.; Orzhekovskaya, E. I.; Selezneva, N. M.; Vasyanina, L. K.; Vorontsov, E. V.; Stash, A. I.; Bel'skii, V. K. *Russ. J. Gen. Chem.* **2002**, 72, 193.

(3) Oh, J. S.; Kim, E. J. U.S. Patent 5,384,424, 1992.

(4) (a) Tani, K.; Kobayashi, K.; Maruyama, T. European Patent 1,258,473, 2001. (b) Patoiseau, J. P.; Autin, J. M.; Cousse, H.; Sales, V.; Tisne-Versailles, J.; Bali, J. P. U.S. Patent 5,091,415, 1992.

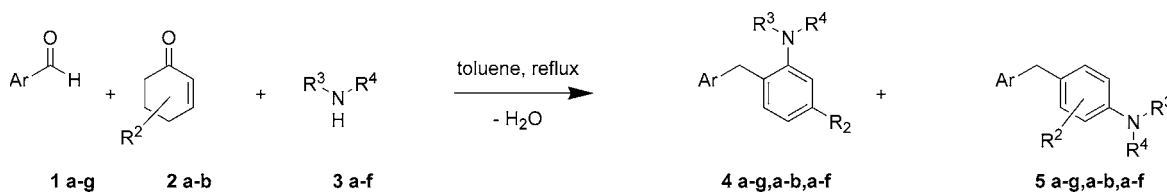
(5) (a) Sukumar, R.; Sabu, K. R.; Lalithambika, M. *Green Chem.* **1999**, 1, 191. (b) Rivera, A.; Torres, O. L.; Leitón, J. D.; Morales-Rios, M. S.; Joseph-Nathan, P. *Synth. Commun.* **2002**, 32, 1407.

(6) (a) Katritzky, A. R.; Lang, H.; Lan, X. *Tetrahedron* **1993**, 49, 7445. (b) Sisko, J.; Weinreb, S. M. *Synth. Commun.* **1988**, 18, 1035. (c) Gassman, P. G.; Drewes, H. R. *J. Am. Chem. Soc.* **1978**, 100, 7600.

(7) (a) Kreher, U. P.; Rosamilia, A. E.; Raston, C. L.; Scott, J. L.; Strauss, C. R. *Org. Lett.* **2003**, 5, 3107. (b) Higham, L. T.; Kreher, U. P.; Raston, C. L.; Scott, J. L.; Strauss, C. R. *Org. Lett.* **2004**, 6, 3257.

(8) Anastas, P. T.; Warner, J. C. *Green Chemistry—Theory and Practice*; Oxford University Press: New York, 1998.

### Scheme 1. New Multicomponent Reaction

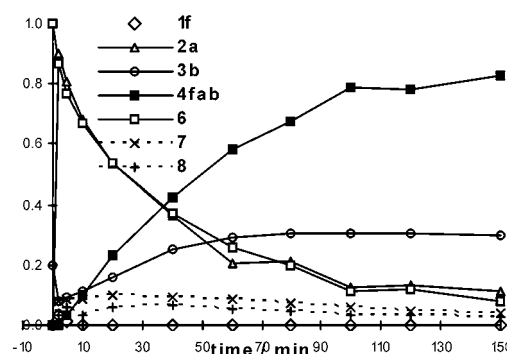


Mixtures of a tertiary amine and a weak acid can catalyze these reactions, presumably by buffering the systems. PhCOOH and DABCO have proven effective in that regard. Reactions can proceed, albeit more slowly, without acid and catalytic base, or with either an acid or base alone (see examples in Table 1). The presence of DABCO, however, afforded improved yields and fewer byproducts.

Regioselectivity usually was high under protocols presented herein. Influences included the catalysts employed and the rate of addition of the enone, but regioselectivity was dictated mainly by the nature of the participating amine. Primary and secondary amines predominantly afforded 2-mono-*N*-substituted and 4-di-*N*-substituted anilines, respectively.

The pathway was explored by NMR-monitoring of reactions as they progressed, without water removal (see Scheme 2) and with variation in the order of combination of the components, to deconvolute the effects of competing equilibria. Predictably, combination of aldehyde **1f** and primary amine **3b** in toluene- $d_8$  led to formation of imine **6** (accelerated in the presence of DABCO/PhCOOH and/or heating). After addition of cyclohexenone **2a** the reaction progressed smoothly. The increase in concentration of product **4fab** was concomitant with essentially collinear decrease in concentration of imine **6** and cyclohexanone **2a**, as illustrated in Figure 1. The minor components provided clues as to the genesis of the aniline functionality: in a minor alternative process, cyclohexenone **2a** reacted with amine **3b** to afford an unstable olefinic imine **8** directly. In the absence of aldehyde, a new resonance signal appeared in the  $^1H$  NMR spectrum

at  $\delta$  4.42 ppm, diagnostic of a methylene group neighbored by an imino nitrogen and a phenyl ring.



**Figure 1.** Relative concentrations in the reaction of furfural (**1f**) with benzylamine (**3b**) and cyclohexenone (**2a**). The reaction was carried out in toluene- $d_8$  at 80 °C, and concentrations were inferred from integrated areas of well-defined  $^1H$  NMR signals for each compound. (Reaction mixture: 1.0 equiv of **1f**, 1.2 equiv of **3b**, 0.5 equiv of DABCO, and 0.55 equiv of PhCOOH in 1 mL of toluene- $d_8$ . 1.0 equiv cyclohex-2-enone added at  $t = 5$  min.)

We propose that the enamine tautomer **9** of the olefinic imine **6** was the key intermediate in the multicomponent reaction. As suggested in Scheme 2, addition of tautomer **9** to imine **6**, followed by elimination of one molecule of amine **3b** and isoaromatization, would afford the product **4fab**. From Figure 1, the crossover point between formation of

### Scheme 2. Postulated Reaction Pathway and Intermediates

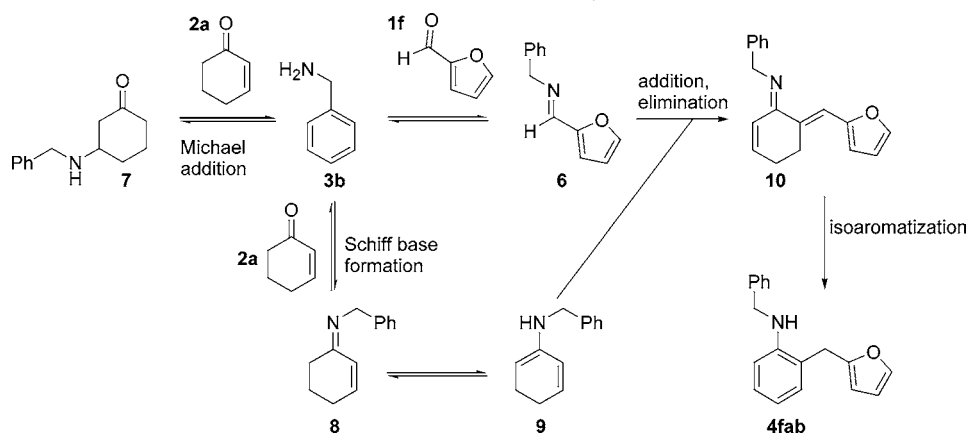



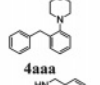
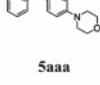



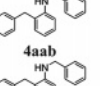



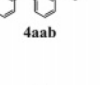



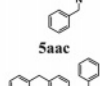



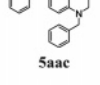



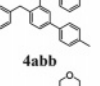



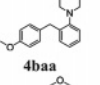
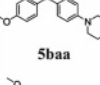



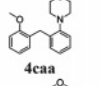
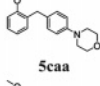



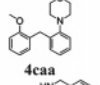
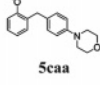



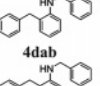



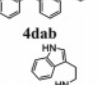



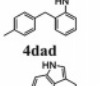



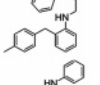



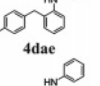



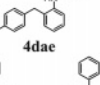



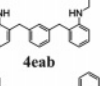



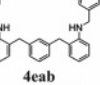



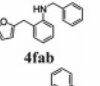



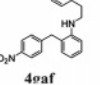


Table 1. Examples

entry	1	2	3	eq. 1:2:3	cat.	time / h	product 4 yield / %	product 5 yield / %
1	 1a	 2a	 3a	1:1:4	a	5	 4aaa	 5aaa
2	 1a	 2a	 3b	1:2:3	-	26	 4aab	-
3	 1a	 2a	 3b	1:3:3	b	20	 4aab	-
4	 1a	 2a	 3c	1:4:3	-	44	-	 5aac
5	 1a	 2a	 3c	1:2.5:1.4	c	8	-	 5aac
6	 1a	 2b	 3b	1:1.2:3	-	20	 4abb	-
7	 1b	 2a	 3a	1:2:3.5	-	48	 4baa	 5baa
8	 1c	 2a	 3a	1:2:4	-	47	 4caa	 5caa
9	 1c	 2a	 3a	1:1:1.4	c	2.5	 4caa	 5caa
10	 1d	 2a	 3b	1:2.6:3	-	36	 4dab	-
11	 1d	 2a	 3b	1:1.5:1.2	c	4	 4dab	-
12	 1d	 2a	 3d	1:2:3	-	24	 4dad	-
13	 1d	 2a	 3d	1:1:1.2	c	1.5	 4dad	-
14	 1d	 2a	 3e	1:2:3	-	24	 4dae	-
15	 1d	 2a	 3e	1:2:1.2	c	4.5	 4dae	-
16	 1e	 2a	 3b	1:3:3	-	24	 4eab	-
17	 1e	 2a	 3b	1:2.25:1.2	c	3.5	 4eab	-
18	 1f	 2a	 3b	1:1:1.2	c	2	 4fab	-
19	 1g	 2a	 3f	1:1.5:1.2	c	4.5	 4oaf	-

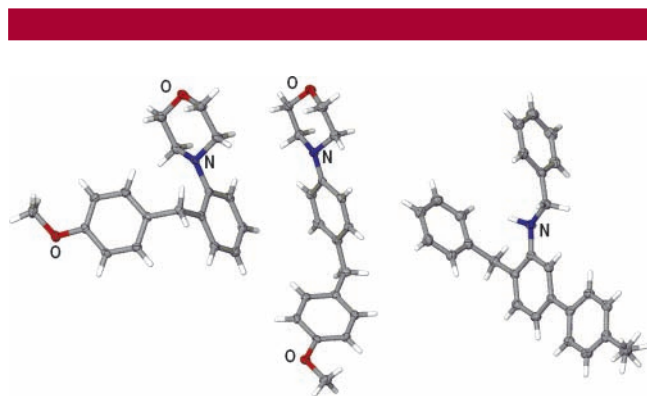
<sup>a</sup> PhCOOH. <sup>b</sup> DABCO. <sup>c</sup> PhCOOH/DABCO (0.55:0.5 relative to aldehyde).

product **4fab** and the depletion of imine **6** and enone **2a** lay midway, highlighting the cleanness of the reaction and the absence of byproducts. The spectra confirmed that, until it was converted to product **4fab**, almost all of aldehyde **1f** was present as its imine derivative **6**. Most of the cyclohexenone **2a**, however, did not react with amine **3b**, indicating that the concentration of **8** (and therefore **9**) was limiting throughout.

Under the conditions, other equilibria were involved. In the absence of aldehyde, it was found that amine **3b** could also add to enone **2a** to form Michael product **7**. When furfural (**1f**) was introduced to a product mixture of amine **3b** and cyclohexenone **2a** in the presence of DABCO and PhCOOH, however, the Michael adduct **7** dissociated and imine **6** accumulated. Thus, under the conditions, **6** was more stable than **7**. This, combined with the aforementioned evidence for low concentrations of enamine **9**, is consistent with the proposal that the reaction involves addition of an enamine of the enone to an imine of the aldehyde, followed by rapid elimination of an amine, to provide intermediate **10**, which undergoes facile isoaromatization to aniline products such as **4fab**.

On occasions when a secondary amine was used, animala were observed.<sup>7a,9</sup> Nonetheless, a set of competing equilibria similar to those depicted in Scheme 2, with irreversible isoaromatization leading to product accumulation, may be envisaged.

Entries 6 and 2 in Table 1 indicated that reactivities of 3-arylcyclohexenone **2b** and cyclohexenone **2a** were comparable, thereby adding weight to the proposed pathway.<sup>10,11</sup> Confirmation of assignment of regiochemistry of product **4abb** arises from the crystal structure of this product presented in Figure 2.



**Figure 2.** Molecular diagrams from single-crystal structure analysis of compounds **4baa**, **5baa**, **4abb** (left to right) with ellipsoids are depicted at the 50% probability level.

The suggested pathway also accounts for the correlation mentioned above, between regioselectivity of the reaction

(9) Katritzky, A. R.; Yannakopoulou, K.; Lang, H. *J. Chem. Soc., Perkin Trans. 2* **1994**, 1867.

and bulkiness of the participating amine. With bulky disubstituted amines, nucleophilic attack on the iminium species of the aldehyde (also sterically constrained) would be more favored from the 4-position than from the crowded 2-position of the tautomeric enamine of the starting enone.

With derivatives of benzaldehyde as starting materials, the reaction has occurred regardless of electron-donating or electron-withdrawing properties of the substituents. A diverse range of aldehydes has been employed, including furfural (**1f**), isophthalaldehyde (**1e**), and various heterocyclic analogues. Applications of the products will be the subject of a future communication. In the presence of cyclohexenone **2a** and benzylamine (**3b**), both carbonyl groups of **1e** reacted to produce a bis-anilino derivative, 1,3-bis(2-benzylaminobenzyl)benzene (**4eab**), in good yield (65%) given the number of transformations involved and the potential scope for competing processes (entry 17, Table 1).

Participating amines investigated successfully so far include benzylamine, aniline, 2-aminomethylpyridine, methyl aminoacetate, tryptamine (all primary) and di(2-methoxyethyl)amine, morpholine, and di-*n*-butylamine (secondary).

To conclude, the new reaction can be performed simply, under relatively uniform conditions and appears to be convergent and predictable, regardless of the diverse array of starting materials that can be employed. Therefore, it offers opportunities for establishment of combinatorial libraries, an aspect that we are exploring. In the context of Green Chemistry, tandem, cascade, and/or multicomponent reactions can be useful if they proceed in good yields with high atom economy and generate little waste. This process could become a useful tool toward establishment of a broader range of significant, but heretofore not conveniently accessible, aniline derivatives.

**Acknowledgment.** We thank the Australian Research Council for funding the establishment and continuation of the ARC Special Research Centre for Green Chemistry (CGC) and for post-graduate scholarships to A.E.R. C.R.S. thanks CSIRO Molecular Science for supporting his secondment to the CGC. Mr. Luke Higham's contribution to crystallographic analysis is acknowledged.

**Supporting Information Available:** Crystal data in CIF format, experimental procedure and full characterization for the all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL0501828

(10) Although in principle, Baylis–Hillman reactions catalyzed by DABCO could occur between an aryl aldehyde (such as benzaldehyde or furfural) and cyclohexenone, such processes were not observed here in the presence of participating amines. Baylis–Hillman reactions do not normally proceed well with enones possessing a  $\beta$ -substituent and to our knowledge no examples exist for substrates that are  $\beta,\beta$ -disubstituted. That the present reaction proceeded readily and in good yield from 3-(4-methylphenyl)-cyclohex-2-enone (entry 6, Table 1) further militates against involvement of a Baylis–Hillman process.

(11) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811.