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Solvent effects in a carbenoid N–H insertion route to triarylamines via 2-diazo-1,3-cyclohexanedione

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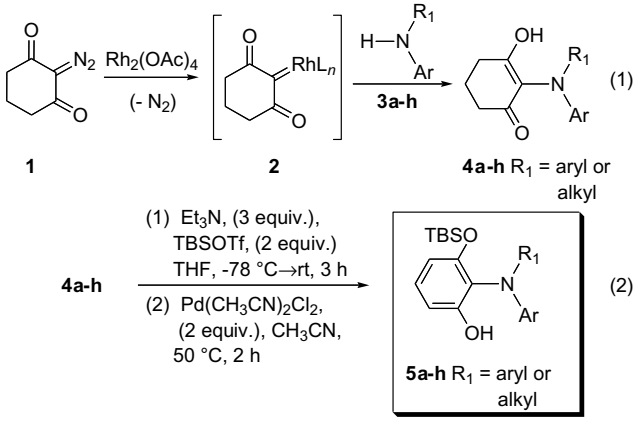
Abstract—The Rh-carbenoid derived from 2-diazo-1,3-cyclohexanedione inserts into the N–H bond of arylalkylamines and diarylamines. A solvent for this reactive carbenoid is suggested. The insertion products undergo a Pd-mediated aromatization to afford alkyldiarylamines and triarylamines.

1. Introduction

The general problem of synthesizing triarylamines, an important class of compounds,[1] has been addressed with impressive success, largely by the groups of Buchwald and Hartwig.[2] In our own laboratory, the $Rh_2(OAc)_4$-catalyzed reactions of dimethyl 2-diazomalonate ('DDM') have been found to give tertiary amines resulting from the insertion of the DDM-derived carbenoid into the N–H bond of various secondary amines.[3] In an extension of that work, the $Rh_2(OAc)_4$-catalyzed reactions of 2-diazo-1,3-cyclohexanedione (**1**) with secondary amines were explored. Analogous carbenoid N–H insertions were indeed found and are reported herein (Scheme 1, Eq. 1).

More importantly vis-á-vis triarylamine synthesis, we also report that the 2-amino-3-hydroxy-2-cyclohexenone moiety of **4** may be aromatized (Scheme 1, Eq. 2), providing a very simple two-step synthesis of triarylamines (and alkyldiarylamines), **5**, in which one aryl group bears differentiable oxygen substituents at positions 2 and 6.

N–H and O–H insertion reactions, although common for carbenoids,[4] have not been well-studied for **1**: the overwhelming majority of reported metal-catalyzed



Scheme 1. N–H insertion/aromatization route to di- and triarylamines.

reactions of **1** are formal cycloadditions of **2** to double- or triple-bonds.[5–23] Pirrung et al.[8] have noted that **2** 'is far more reactive than many previously-studied carbenoids'. Because of this, solvents which cannot be used in Rh-catalyzed reactions of **1** are CH_2Cl_2, $ClCH_2CH_2Cl$, THF, PhF, benzene, CH_3CN, dimethoxyethane, nitromethane, pentane, and hexafluorobenzene.[8,22] Therefore, reactions of **1** are nearly always conducted in the absence of ordinary solvent, with the substrate in excess acting as solvent.

2. Results and discussion

Insertions of **1** into the N–H bond of arylalkylamines or diarylamines are reported in Table 1.[24] We briefly searched for a solvent, so that the range of usable solid

Keywords: Triarylamines; Rhodium carbenoid; N–H insertion; Aromatization; $Rh_2(OAc)_4$; $Pd(CH_3CN)_2Cl_2$; Solvent effect.
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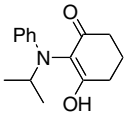
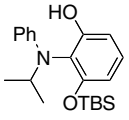
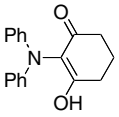
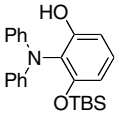
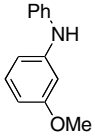
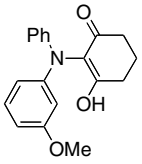
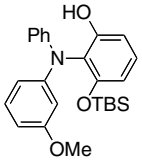
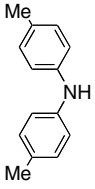
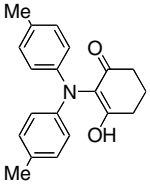
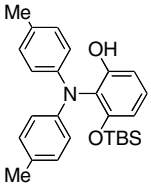
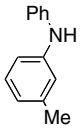
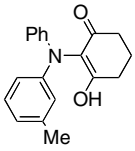
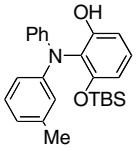
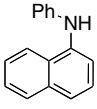
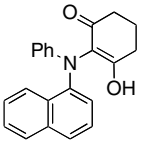
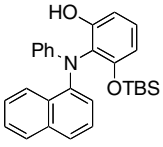
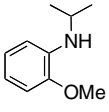
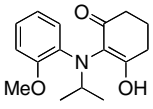
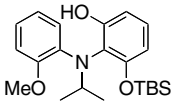
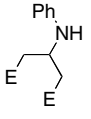
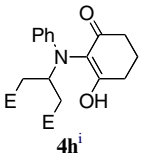
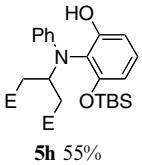
Table 1. Synthesis of di- and triarylamines by N–H insertion/aromatization[a]

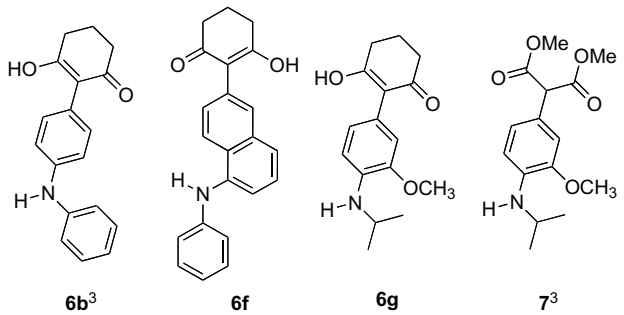
Entry	Reactant	Insertion conditions	N–H insertion product	Aromatization product
1[b]	 **3a**	(i) PhF, rt, 4 h;[c] (ii) no solvent, rt, 4 h	 **4a** (i) 35%; (ii) 65%	 **5a** 60%
2[b]	 **3b**	No solvent, 55 °C, 30 min	 **4b**[d] 75%	 **5b** 57%, 79%[e]
3	 **3c**	No solvent, 75 °C, 30 min	 **4c** 70%	 **5c** 59%
4	 **3d**	(i) No solvent, 85 °C, 30 min; (ii) Hexachloroacetone rt, 12 h[f]	 **4d** (i) 60%; (ii) 66%	 **5d** 55%
5	 **3e**	No solvent, rt, 4 h	 **4e** 50%	 **5e** 60%
6	 **3f**	No solvent, 65 °C, 2 h	 **4f** 33%[g]	 **5f** 44%
7	 **3g**	No solvent, rt,18 h	 **4g**[h,i]	 **5g** 45%
8	 **3h**, E = CO_2Et	No solvent, rt, 4 h	 **4h**[i]	 **5h** 55%

[a] All yields refer to isolated pure products.
[b] Ref. 3.
[c] **3a**:**1** = 4:1.
[d] A 17% yield of **6b** was also obtained.
[e] 6 equiv Et_3N, 3 equiv TBSOTf and 5 equiv $Pd(CH_3CN)_2Cl_2$ were used.
[f] **3d**:**1** = 2:1.
[g] A small amount of **6f** was also obtained.
[h] Yield of **4g** was ca. 33%, but an unidentified contaminant could not be removed. A ca. 25% yield of **6g** was also obtained.
[i] This material was used in the next step without full purification.

amines would not be limited by melting point. A solvent, fluorobenzene, was tried in the case of *N*-isopropylaniline, **3a**, but it competed with **3a** for **2**, leading to a much lower yield of N–H insertion product **4a** (Table 1, entry 1). In CH_2Cl_2 solvent, treatment of **1** with *N*-cyclohexylaniline and $Rh_2(OAc)_4$ resulted in reaction of **2** exclusively with the solvent, forming 2-chloro-3-chloromethoxy-2-cyclohexenone[26] (which slowly hydrolyzes to 2-chloro-1,3-cyclohexanedione).[8] Despite the reactivity of **2** toward the C–Cl bonds of CH_2Cl_2, hexachloroacetone (HCA) was tried as an N–H insertion solvent (entry 4), with good results. We could not detect any evidence of reaction of **1** with this solvent. HCA is therefore a rare example of a compound with which **1** does not react. As such, it may have some promise as a reaction solvent for **1**. HCA is known to react with amines, however,[27,28] and so its utility as a solvent for the type of N–H insertions reported here would not be expected to be general. (Indeed, the attempted Rh-catalyzed insertion of **1** into the N–H bond of bis(2,6-dimethoxyphenyl)amine in HCA failed because the amine reacted with HCA). The use of HCA as a solvent for the reactions of **1** with other substrates is, however, worth considering.

Formal insertion of **2** into an aromatic C–H bond was a side reaction in several N–H insertion reactions (entries 2, 6, and 7). The structures, deduced by NMR studies, of C–H insertion by-products accompanying **4b**, **4f**, and **4g** (viz. **6b**,[3] **6f**, and **6g**) are shown in Figure 1. The assignment of **6g** as the product of C–H insertion at C4 rather than C5 was aided by comparison of its ^{13}C NMR spectrum with that of authentic **7**.[3] The chemical shifts of the six aromatic carbons of **6g** and **7** differed by an rms average of 1.0 ppm.

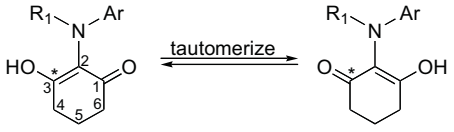
Equilibration of the enol (Eq. 3) is slow on the NMR timescale in $CDCl_3$, as the two oxygen-bearing carbons are nonequivalent in the room temperature ^{13}C NMR spectra of all compounds **4**. For example, in **4b**, the carbonyl carbon absorbs at 194.9 ppm and the enol 'alcohol' carbon absorbs at 175.1 ppm. The carbons adjacent to these are also nonequivalent (27.8 and 37.7 ppm). In some cases, the rate of this equilibrium was faster. For example, for **4c** in $CDCl_3$, the carbonyl carbon signal and the enol 'alcohol' carbon signal appeared together as an extremely broad signal at roughly 188 ppm. The adjacent carbons (27.8 and 37.7 ppm for **4b**) appeared as a broad peak at 32.6 ppm.



6b[3] **6f** **6g** **7**[3]

Figure 1. By-products resulting from formal C–H insertions.

X-ray crystallography of **4b** further confirmed the enol structure postulated for all **4**. Despite the arduous structure solution and refinement (four unique molecules per unit cell, and disorder at C5 of the cyclohex-2-enone ring), the OH hydrogen was located. It participates in hydrogen bonding to the carbonyl oxygen on a neighboring molecule. Nitrogen is not involved in hydrogen bonding. The average plane of the cyclohexenone ring is twisted 91.6(1)° out of the plane defined by the three N-bound carbons. The analogous twists for the two phenyls are 9.5(1)° and 67.7(1)°.



(3)

The N–H insertion products were, on average, hard to purify. Small amounts of unidentified by-products stubbornly resisted chromatographic separation. In addition, these compounds, while stable in the solid state, degraded quickly in solution. Fortunately, it was found that the next step—aromatization of the 3-hydroxy-2-cyclohexenone ring—led to products, which were more easily obtained with analytical purity.

The use of DDQ as an aromatization reagent led to undesired C–N cleavage products. Aromatization of the insertion products **4a**–**h** was achieved under mild conditions by adapting the recently reported procedure of Ishikawa et al.[29] for the aromatization of enamines using stoichiometric quantities of $Pd(CH_3CN)_2Cl_2$. Treatment of **4** with *tert*-butyldimethylsilyl triflate (TBSOTf) produced, presumably, an enol silyl ether, which was not isolated. In the same pot, treatment with two equivalents of the Pd reagent afforded the aromatized product, **5**, in good, but not excellent, yield.[30] In one case the use of a large excess of the Pd reagent (5 equiv) resulted in a somewhat better yield (entry 2).

In sum, the insertion of **1** into the N–H bond of an alkylarylamine or diarylamine, followed by Pd-mediated aromatization described here provides a simple, mild route to novel di- and triarylamines.

Acknowledgements

We heartily thank Dr. Thomas Albrecht-Schmitt and Mr. Richard Sykora for collecting, solving and refining the unexpectedly nettlesome crystal structure of **4b**. Many helpful discussions with Dr. Minmin Yang are gratefully acknowledged.

Supplementary data

Full experimental details, including spectroscopic data, ORTEP of **4b**. Crystallographic data for **4b** have been deposited with the Cambridge Crystallographic Data

Centre as supplementary publication number CCDC 243405. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0)1223 336033 or email: deposit@ccdc.cam.ac.uk]. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.01.131.

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24. General procedure for reaction of **1** with amines: Under a nitrogen atmosphere, a mixture of 1.00 mmol of **1**[25] and 5 mmol of diarylamine or alkylarylamine (liquid at rt) was stirred until homogeneous. Solid amines were brought to a few degrees above their mp. To the mixture of **1** and **3** was added 0.0050 mmol of $Rh_2(OAc)_4$ and the stirring continued at rt for 4 h or for 0.5–3 h in the case of molten amines. Silica gel chromatography using EtOAc–hexanes 1:30 (v/v) removed excess secondary amine. A step-gradient to EtOAc–hexanes 1:4 (v/v) afforded the N–H insertion product. Data for 2-(di-*p*-tolylamino)-3-hydroxy-2-cyclohexenone, **4d**. ^{1}H NMR (400 MHz, $CDCl_3$): 7.03 (d, $J = 8.0$ Hz, 4H), 6.92 (d, $J = 8.5$ Hz, 4H), 2.67 (t, $J = 6.3$ Hz, 2H), 2.48 (t, $J = 6.6$ Hz, 2H), 2.28 (s, 6H), 2.07 (quintet, $J = 6.5$ Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 194.5, 172.5, 144.0, 132.1, 129.8, 122.0, 120.7, 37.7, 27.5, 20.7, 20.2.
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30. General procedure for aromatization of 2-amino-3-hydroxy-2-cyclohexenone derivatives: 0.1–0.3 g of the N–H insertion product was dissolved in 5 mL of dry THF. Triethylamine (3 equiv) were added. The solution was cooled to −78 °C, and 2 equiv of TBSOTf were added dropwise via syringe. This solution was stirred for 3 h, eventually reaching rt. Acetonitrile, 5 mL, and 2 equiv of $Pd(CH_3CN)_2Cl_2$ were added, the mixture warmed to 50 °C, and stirred for 2 h. After cooling to rt, the mixture was filtered, 10 mL satd aq $NaHCO_3$ was added, extracted with EtOAc (3 × 10 mL), the combined extracts dried over Na_2SO_4, filtered, concentrated and subjected to silica gel chromatography, using EtOAc–hexanes 1:8 (v/v), to afford the aromatized product. Data for 2-*tert*-butyldimethylsiloxy-6-hydroxy-*N*,*N*-di-*p*-tolylaniline, **5d**. Anal. Calcd for $C_{26}H_{33}NO_2Si$: C, 74.42; H, 7.93; N, 3.34. Found: C, 74.19; H, 7.99; N, 3.32. ^{1}H NMR (250 MHz, $CDCl_3$): 7.25 (t, $J = 8.2$ Hz, 1H), 7.13 (m, 8H), 6.78 (dd, $J = 8.3$, 1.3 Hz, 1H), 6.64 (dd, $J = 8.3$, 1.3 Hz, 1H), 5.97 (s, 1H), 2.44 (s, 6H), 0.87 (s, 9H), 0.24 (s, 6H). ^{13}C NMR (63 MHz, $CDCl_3$): 155.4, 154.4, 143.9, 131.4, 129.8, 128.3, 123.5, 120.4, 111.3, 108.4, 25.6, 20.8, 18.2, −4.0.