Aniline Synthesis

Anilines Made Easily: From Aldehydes to Tri-, Tetra-, and Pentasubstituted Anilines in Two Steps**

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Dedicated to Professor Boy Cornils on the occasion of his 65th birthday

Polysubstituted anilines play a central role as building blocks in synthetic chemistry. Major technical applications include their use as intermediates in the manufacture of agrochemicals, pharmaceuticals, dyes, pigments, and rubber chemicals.[1] Although anilines have become accessible by new methods—in particular catalyzed by transition metals—in recent years, most technically feasible syntheses still rely on classical approaches. While sequential electrophilic nitration and reduction suffers from the relatively harsh reaction conditions,[2] nucleophilic aromatic amination requires the presence of special substituents.[3] The recently developed palladium-catalyzed[4] (Buchwald–Hartwig amination) and copper-catalyzed[5] aminations of aryl halides provide a general entry to this class of compounds. However, for these reactions as well as for other known syntheses of polysubstituted anilines, aromatic reactants with a defined substitution pattern are needed. In most cases, these starting materials are synthesized in numerous steps generating several equivalents of waste and salt as by-products.

Over the last years we have been involved in the development of new syntheses of amino compounds with special regard to transition-metal-catalyzed hydroaminations,[6] hydroaminomethylations,[7] and amidocarbonylations.[8] Recently, we reported on novel multicomponent reactions (MCRs)[9] of amides and aldehydes with dienophiles for the straightforward synthesis of a large variety of carbo- and heterocyclic amides.[10] As shown in Scheme 1, the underlying mechanism involves the intermediacy of an Oppolzer–Overman-type 1-(*N*-acylamino)-1,3-butadiene, which easily undergoes Diels–Alder addition with an electron-deficient dienophile.[11] The synthesized three-component adducts exhibit a high degree of diversity, which is based

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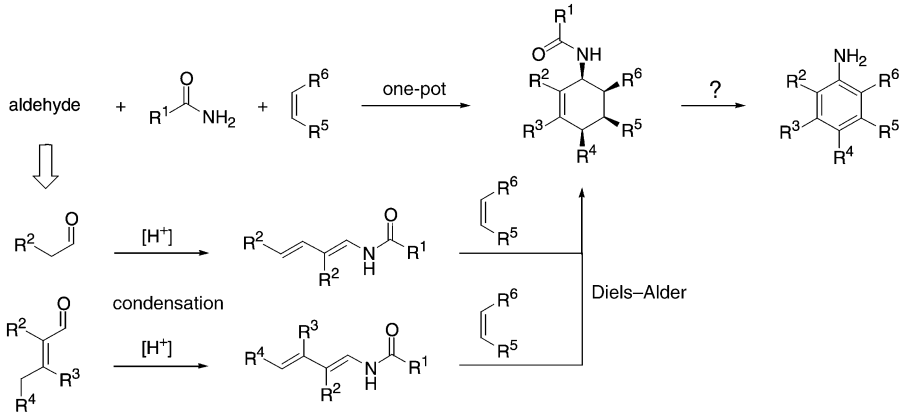


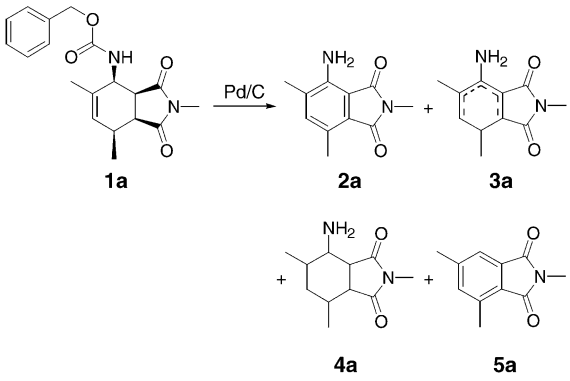
Scheme 1. Three-component-coupling reaction of amides, aldehydes, and dienophiles and the envisioned aromatization to give anilines.

upon structural variations of the simple, ubiquitous components—carboxamides, aldehydes, and olefins.

We considered the new three-component coupling products useful intermediates for the synthesis of anilines. Obviously, such a strategy constitutes a short and highly convergent synthetic approach. Although syntheses of arenes based on transition-metal-catalyzed cyclization reactions with alkynes[12] and Diels–Alder reactions with heterodienes[13] have been reported in the past, the operational difficulty and the laborious synthesis of the precursors diminish their general use. Here, we wish to report a novel reaction sequence for the synthesis of substituted anilines by the combination of a three-component-coupling reaction and a new transition-metal-catalyzed aromatization step (Scheme 1). To the best of our knowledge, such a strategy has not been used previously for the synthesis of anilines.

Initial studies on the aromatization of three-component coupling products of different aliphatic and aromatic amides in the presence of stoichiometric quantities of sulfur or catalytic amounts of Pd/C and various other oxidants gave low conversion or complex product mixtures (yield of anilines $< 5\%$). Therefore, we considered facilitation of the aromatization process by using a quasi-intramolecular[14] hydrogen transfer onto a powerful hydrogen acceptor within the molecule. The use of *O*-benzyl carbamate as the amide component could yield a coupling product that would fulfill this requirement. Reaction of propionaldehyde, *O*-benzyl carbamate ($CbzNH_2$, $R^1 = BnO$), and maleimide furnished 4-*N*-(benzyloxycarbonyl)aminohexahydro-1*H*-isoindole (**1a**) in 79% yield. Next, imide **1a** was subjected to different cleavage procedures [Eq. (1)]. When **1a** was heated at reflux in the presence of Pd/C and cyclohexene (as a hydrogen donor) in ethanol,[15] a mixture of products was afforded (Table 1). Three isomeric amino-substituted cyclohexenes (formed in 26% overall yield (6:7:13)) and the targeted oxidized species, aniline **2a** (28%), were identified as major products. When the reaction conditions were optimized, **2a** was obtained in excellent yield (91%).

In the presence of stronger hydrogen donors (H_2,[16] HCO_2H[17]), saturated cyclohexane **4a** was formed in moderate yield. A significant increase in the yield of aniline **2a** was observed when triglyme was employed as the solvent and the reaction was conducted at higher temperatures. The cyclohexene moiety in **1a** itself can act as an efficient hydrogen donor for the debenzylation of the carbamate (Table 1, entries 8–10),



(1)

Table 1: Palladium-catalyzed aromatization of 4-*N*-(benzyloxycarbonyl)aminohexahydro-1*H*-isoindole **1a** (GC yields).

Entry	Pd [mol%]	Solvent	H_2 donor	*t* [h]	*T* [°C]	Yield [%] **2a**	Yield [%] **3a/4a/5a**
1	32	EtOH	C_6H_{10}[a]	0.16	80	28	26/–/–
2	32	EtOH	C_6H_{10}[a]	16	80	37	13/–/7
3	32	MeOH	H_2[b]	24	25	–	–/35/–
4	32	MeOH	HCO_2H[c]	0.16	25	–	–/25/–
5	16	EtOH	C_6H_{10}[a]	24	80	40	
6	8	EtOH	C_6H_{10}[a]	24	120	36	
7	8	EtOH	–	24	120	30	
8	8	triglyme	–	24	120	50	
9	8	triglyme	–	24	140	71	
10	8	triglyme	–	24	140	95[d]	
11	4	triglyme	–	24	140	65[d]	

Conditions: **1a** (0.5 mmol), 10% Pd/C, solvent (10 mL), ACE pressure tube; [a] 200 mmol; [b] 15 bar; [c] 10 equiv; [d] Large scale: **1a** (3 mmol).

which supersedes the use of an extra hydrogen donor. This unprecedented reaction pattern involves H_2 elimination and Cbz cleavage. As Cbz cleavage cannot be effected without concomitant supply of hydrogen atoms from the ring aromatization, we propose the operation of a domino dehydrogenation/Cbz-cleavage process.[18] While both the palladium-catalyzed dehydrogenation[19] and the palladium-catalyzed Cbz-cleavage from amines[15–20] have been investigated as

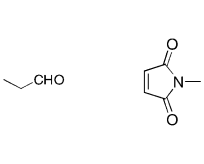
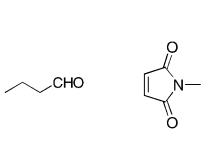
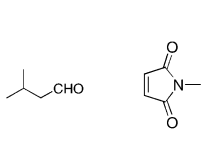
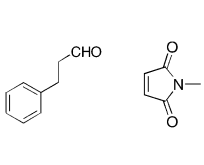
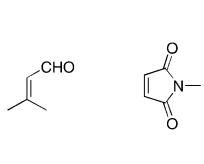
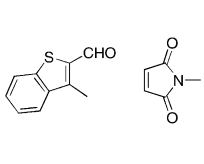
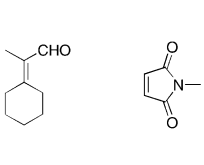
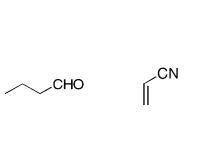
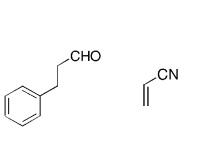
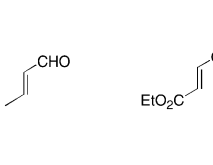
separate processes, no procedure involving the concurrent operation of both transformations has been reported so far.

We set out to extend the methodology to other *N*-(Cbz)aminocyclohexenes. Therefore, a variety of three-component adducts of *O*-benzyl carbamate, aldehydes, and dienophiles were prepared. Table 2 (middle) shows a selection of 10 adducts with diverse substituents. Regarding the aldehyde component, simple aliphatic (with an α-CH_2 moiety) and α,β-unsaturated (with a γ-hydrogen) aldehydes bearing linear or branched alkyl, aryl, or heteroaryl substituents were employed. While simple aldehydes lead to adducts with equivalent substituents on C4 and C6, reactions with α,β-unsaturated aldehydes are not subject to this restriction. Compounds **1f** and **1g** (Table 2, entries 6 and 7) illustrate the potential for the construction of anellated ring systems. Further diversity of the three-component adducts was attained by employing different dienophiles such as *N*-methyl maleimide, acrylonitrile, and diethyl fumarate. Apart from benzothiazole **1f** (44%), the three-component adducts were isolated in good yields (65–89%) without further optimization. NMR spectra established the *syn* configuration of the cycloadducts, as expected from a selective *endo* Diels–Alder reaction of the all-*trans* aminodiene.[21] However, reactions with diethyl fumarate gave an equimolar mixture of two isomers with an overall yield of 67% (Table 2, entry 10).

The domino dehydrogenation/Cbz-cleavage reaction of **1a–j** cleanly afforded the desired anilines (Table 2). Aromatization of imides **1a–f** yielded substituted 4-amino-1,3-dioxo-2,3-dihydro-1*H*-isoindoles **2a–g** (entries 1–7). The employment of 2-cyclohexylidenepropionaldehyde[22] proves the possibility to access hexasubstituted aminobenzenes in only two (!) reaction steps (entry 7). With dienophilic acrylonitrile, substituted 2-aminobenzonitriles (**2h**, **2i**) were accessed in a straightforward manner (entries 8, 9). These compounds constitute important intermediates for the synthesis of pharmaceuticals; for example, simple reaction with α-halocarboxylic acids and subsequent reduction affords 1,4-benzodiazepines.[23] Both isomers of diester **1j** gave the desired aniline in equivalent yields (entry 10).

In conclusion, we have developed a new, highly efficient strategy for the synthesis of substituted anilines. A palladium-catalyzed

Table 2: Pd/C-catalyzed synthesis of polysubstituted anilines.

Entry	Aldehyde	Dienophile	Coupling product	Yield [%]	Aniline	Yield [%]
1			**1a**	79	**2a**	91
2			**1b**	88	**2b**	79
3			**1c**	74	**2c**	80
4			**1d**	73	**2d**	91
5			**1e**	87	**2e**	64
6			**1f**	44	**2f**	78
7			**1g**	45	**2g**	40
8			**1h**	68	**2h**	63
9			**1i**	66	**2i**	62
10			**1j**	67	**2j**	78

aromatization of three-component-coupling products, which is based on a new transfer hydrogenation reaction, is the key step of the described method. The sequential combination of a three-component-coupling reaction and a domino deprotection/aromatization reaction leads to the straightforward synthesis of polysubstituted anilines with diverse substitution patterns.[24] The overall procedure utilizes simple, readily available starting materials and is unique in that it allows the (regio)selective introduction of substituents in one *ortho*, one *meta*, and *para* position, as well as electron-deficient substituents in the other *ortho* and *meta* positions. To the best of our knowledge, this type of tri-, tetra-, and pentasubstituted anilines cannot be accessed by any other methods with similar efficiency.

Experimental Section

General procedure for the preparation of **1**: A mixture of *O*-benzyl carbamate (15 mmol), *p*-toluenesulfonic acid·H_2O (2 mol%), aldehyde (15 mmol), Ac_2O (15 mmol), maleimide (11 mmol), and *N*-methylpyrrolidone (10 mL) was sealed in an ACE pressure tube and stirred at 120°C. After 24 h the solvent and other volatile compounds were removed by high-vacuum distillation. Silica gel flash chromatography (heptane/ethyl acetate) of the residue afforded the three-component-reaction adducts as air-stable solids.

With α,β-unsaturated aldehydes, reactions were run in the presence of 7.5 mmol aldehyde and without Ac_2O. Reactions with acrylonitrile used a fourfold excess of the dienophile and required 4 d for completion.

General procedure for the synthesis of **2**: A 100-mL flask was charged with a mixture of carbamate **1** (2.9 mmol), Pd/C (10% Pd on C, 8 mol%), and triglyme (20 mL), equipped with a reflux condenser, and heated to 140°C. After 6–64 h the solution was filtered through a Celite pad, and solvent and other volatile compounds were removed by high-vacuum distillation. The residue was subjected to silica gel flash chromatography (heptane/ethyl acetate).

1a: According to the general procedure for **1**, *O*-benzyl carbamate (2.27 g, 15 mmol), propionaldehyde (0.87 g, 15 mmol), acetic anhydride (1.4 mL, 15 mmol), and *N*-methylmaleimide (1.28 g, 11.25 mmol) were employed. SiO_2 chromatography (hept/EtOAc 3:1): $R_f = 0.15$. 79% yield of isolated product (white solid). M.p. 62–66°C. IR (KBr): $\tilde{\nu} = 3395$ br vs, 3064 w, 3033 w, 2937 m, 1769 m, 1705 br vs, 1514 vs, 1437 s, 1384 s, 1336 s, 1287 s, 1232 s, 1045 s, 912 w, 836 m, 781 m, 749 m, 699 s, 662 w, 594 m, 531 cm^{-1}; MS (EI): 342 ([*M*]$^+$, 1%), 251 ([*M*−Bn]$^+$, 5%), 233 ([*M*−BnO]$^+$, 4%), 207 (93%), 122 (23%), 107 ([BnO]$^+$, 17%), 91 ([Bn]$^+$, 100%, no other peaks of >5%; HRMS: calcd for $C_{19}H_{22}N_2O_4$: 342.15796; found: 342.15788; NMR ([D$_6$]DMSO): ^{1}H $\delta = 7.44$–7.34 (m, 5H, Ph), 6.96 (d, 9.3 Hz, 1H, N*H*), 5.36 (s, 1H, C=), 5.15 (s, 2H, CH_2), 4.36 (m, 1H, NHC*H*), 3.33 (dd, 6.2/8.4 Hz, 1H, NHCHC*H*), 3.11 (t*, 7.7 Hz, 1H, CH_3CHC*H*CO), 2.78 (s, 3H, N*Me*), 2.49–2.43 (m, 1H, MeC*H*), 1.62 (s, 3H, *Me*C=), 1.28 ppm (d, 7.4 Hz, 3H, *Me*CH); ^{13}C{^{1}H} $\delta = 178.9$ and 177.1 (2 *C*O); 155.6 (*C*O_2), 137.3 (Me*C*=), 136.9, 128.4, 127.9, 127.7, and 127.1 (*C*H= and Ph), 65.8 (*C*H_2O), 49.7 (NH*C*H), 44.1 and 43.9 (NHCH*C*H*C*H), 29.6 (Me*C*H), 24.3 (N*Me*), 18.0 and 16.8 ppm (*Me*C= and *Me*CH).

2a: According to the general procedure for **2**, carbamate **1a** (1.0 g, 2.9 mmol) and Pd/C (0.25 g, 10% Pd on C) were employed. SiO_2 chromatography (hept/EtOAc 3:1): $R_f = 0.15$. 91% yield of isolated product (yellowish solid). M.p. 185–187°C. IR (KBr): $\tilde{\nu} =$ 3475, 3370 vs, 3200, 2924 w, 1740 s, 1690 s, 1642 s, 1614 m, 1596 m, 1492 s, 1441 s, 1382 m, 1370 m, 1313 w, 1268 s, 1235 m, 1159 w, 1125 w, 1024 s, 996 s, 761 s, 615 m, 560 cm^{-1}; MS (EI): 204 ([*M*]$^+$, 100%), 189 ([*M*−NH]$^+$, 18%), 147 ([*M*−CO−NMe]$^+$, 19%), 119 ([*M*−2CO−NMe]$^+$, 42%), no other peaks of >5%. HRMS: calcd for $C_{11}H_{12}N_2O_2$: 204.08890; found: 204.08987; NMR ([D$_6$]DMSO): ^{1}H $\delta = 7.07$ (s, 1H, Ph), 6.01 (s, 2H, NH_2), 2.91 (s, 3H, N*Me*), 2.35 (s, 3H, *Me*), 2.13 ppm (s, 3H, *Me*); ^{13}C{^{1}H} $\delta = 169.6$ and 169.5 (2 *C*O), 143.2, 130.2, 125.8, 124.3, and 109.2 (5*C* of Ph), 137.7 (*C*H of Ph), 23.0, 17.0, and 15.9 ppm (3 M*e*).

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[14] The net balance constitutes an intramolecular consumption of two hydrogen atoms for the Cbz-cleavage and the release of two further hydrogen atoms. Although the hydrogen-transfer process is likely to proceed in intramolecular fashion, we cannot exclude the competitive operation of intermolecular pathways.

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