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Alkylation of aromatic amines by *tert*-enamides: Direct access to protected aminals

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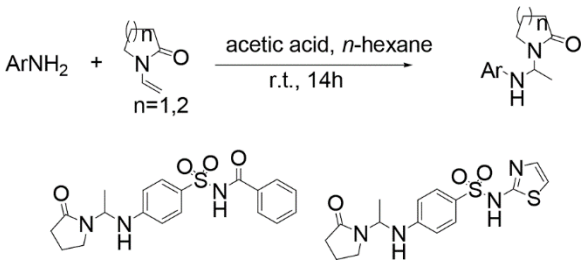
Supplemental data (full experimental details and characterization of title compounds) for this article can be access on the publisher's website. <TQ: The publisher's website will be a live link.>

ABSTRACT

Reaction of aromatic amines with tertiary enamides was carried out in *n*-hexane in the presence of acetic acid as an inexpensive and green catalyst at room temperature. This protocol provides the protected aminals via Markovnikov addition reaction with high to excellent yields

and regiospecificity. In addition, this procedure was expanded for the synthesis of aminals from commercially available sulfa drugs such as sulfathiazole and sulfabenzamide.

GRAPHICAL ABSTRACT



KEYWORDS: aromatic amines, markovnikov addition, protected aminal, *tert*-enamide

Introduction

Compounds containing nitrogen atom are of great importance because of their interesting properties and wide applications in pharmaceutical chemistry. C–N bond construction is of significant importance as it opens windows for introducing nitrogen atom in organic molecules.[1–3] Aminals, a category of compounds containing geminal nitrogens, are useful intermediates in organic chemistry as surrogate of imines and were applied extensively as efficient electrophiles for nucleophilic addition reactions.[4–8] The reactivity and stability of aminals tolerates with the substitutions on the nitrogens and the aminal carbon atom. Although cyclic aminals are stable and observed in the structure of many natural products,[9–12] acyclic aminals suffer from their instability and difficulties in their production. Usually, electron withdrawing groups on the nitrogen atoms of aminals increase their stability. Recently, several interesting methods were reported for the synthesis of acyclic aminals including $FeCl_3$/TBHP catalyzed sp^3C–H amination of amides and lactams with aromatic amines,[13] direct condensation of aldehydes with amines,[14] amides[15] and lactams[16] in the presence of a catalyst, Brønsted

acid-catalyzed imine amidation,[17] and one-pot three-component reaction of aldehydes, aromatic amines and lactames/amides.[18]

Enamides, as electron-riched alkenes, have been extensively applied as nucleophile in many organic transformations.[19–21] They were widely applied in Povarov reaction.[22,23] In addition, their applications in the synthesis of polymers were extensively investigated.[24] Recently, especial attentions are denoted toward electrophilic properties of enamides using Lewis or Brønsted-Lowry acid catalysts.[25,26] In the presence of an acid catalyst, enamides usually protonated to provide the corresponding imminium ions, which are highly reactive components toward nucleophiles.[27] Recently, reaction of enamides with *in situ* prepared dithiocarbamic acids is reported by our group.[28,29] Also, Friedel-Crafts alkylation of indoles and naphtholes with enamides in the presence of various catalysts is frequently reported by Ji,[30,31] Hou,[32] and Zhang.[33] Furthermore, direct alkylation of amines with enamides using I_2,[34] $NaHSO_4$[35] and triarylaminium salt [tris(4-bromophenyl)-aminium hexachloro-antimonate ($TBPA^{+}$ •$SbCl_6^-$)][36] were reported for the synthesis of aminals. However, synthesis of stable aminals via a simple and efficient procedure provides a great potential in synthetic organic chemistry. Here, we report an efficient and facile procedure for the synthesis of aminals from enamides and amines in the presence of acetic acid in *n*-hexane (Scheme 1).

Results and discussion

Reaction of aniline **1a** with *N*-vinylpyrrolidone **2a** in the presence of acetic acid was considered as model reaction for the optimization of the reaction conditions. Various polar and nonpolar solvents were screened and the results are summarized in **Table 1**. Although good to high yield of aminal **3aa** was obtained in acetonitrile, ethylacetate, methanol, toluene, CH_2Cl_2

and THF, the best yield was obtained in *n*-hexane (98%) (**Table 1**). By using water as reaction medium, high yield of product was obtained (65%). Also, we observed that 1 equiv. of acetic acid in organic solvents and water gave the highest yield. By increasing or decreasing the amount of acetic acid in water, lower yields of **3aa** were obtained. In addition, we observed that the best yield was obtained at room temperature.

After optimization of the reaction conditions, the generality of this protocol was examined using various amines and enamides (**Table 2**). We observed that aromatic amines containing an electron-withdrawing group on the phenyl ring afforded quantitative yields. Also, excellent yield was obtained with aniline. Good to excellent yields were obtained using *p*-toluidine and *p*-anisidine. No aminal was obtained when 1,4-phenylenediamine was applied in the reaction. In addition, the corresponding aminals were obtained in high yields from *p*-aminoacetophenone (**Table 2**, entries 19 and 20). Highly deactivated 2,4-dinitroaniline was also applied in this protocol with no result (**Table 2**, entry 11). Aliphatic amines are not suitable substrates in this protocol (**Table 2**, entry 12). Also, thiourea, benzyl carbamodithioate and guanidine afforded no products (**Table 2**, entries 13–15). Electron-riched arenes such as 2-naphthol and phenol do not react with enamides using optimized reaction conditions. In most of the cases, the pure product was precipitated in the reaction mixture and collected by simple filtration. Reusing the filtrate afforded the corresponding product, albeit in lower yield (60% for **3ba**). Generally, higher yields were obtained for *N*-vinylcaprolactam in comparison to *N*-vinylpyrrolidone. The products were characterized by IR, ^{1}H NMR, ^{13}C NMR and CHN analysis.

After successful derivatization, this protocol was applied for the synthesis of aminals from sulfa drugs such as sulfabenzamide and sulfathiazole. We observed that the aminals of sulfabenzamide (**4a**) and sulfathiazole (**4b**) were obtained in 79 and 89% isolated yield under

optimized reaction conditions, respectively (Scheme 2). Due to the unstability of the aminals in aqueous medium for prolong times, these protected sulfa drugs may be applied for the preparation of novel drugs with long time effect on human bodies.

A proposed mechanism for this transformation is depicted in Scheme 3. It is conceivable that the initial event is the formation of the iminium intermediate **A** from *N*-vinyl pyrroilidone and acetic acid.[14] Subsequent nucleophilic attack of the amine to the iminium intermediate afforded intermediate **B** which then provided the corresponding aminal after hydrogen transfer. The higher yields in hexane compared to water and other solvents may be attributed to the higher stability of the aminals in nonpolar solvents compare to polar protic and aprotic solvents. Also, the lower yields of the aminals for electron-riched anilines can be attributed to the instability of the product in the reaction mixture due to the high electron density on the nitrogen atom which accelerated imine formation by elimination of the pyrrolidone ring.

Conclusion

In conclusion, an efficient procedure for the synthesis of protected aminals from commercially available amines and tertiary enamides via Markovnikov addition reaction in *n*-hexane catalyzed by acetic acid at room temperature is described. This protocol provides the aminals containing gamma- and epsilon-lactams with high to excellent yields and regiospecificity. Higher yields were obtained in this protocol compared to previously reported methods using molecular iodine, $NaHSO_4$ and $TBPA^+ \bullet SbCl_6^-$ as catalyst. Also, this procedure was applied successfully for the synthesis of aminals from commercially available sulfa drugs such as sulfathiazole and sulfabenzamide. According to the known biological activities of sulfa drugs and lactams, the presence of these functionalities in a molecule may have synergic effects

to provide a new family of compounds with interesting biological activities in pharmaceutical industry.

Experimental

General procedure for the alkylation of anilines with enamides

To a magnetically stirred solution of enamide (1.2 mmol) and aromatic amines (1 mmol) in *n*-hexane (3 mL), was added acetic acid (1 mmol, 0.06 mL). The reaction mixture was stirred at room temperature for 14 h. Completion of the reaction was monitored by TLC (ethyl acetate/petroleum ether, 1/3). The products were precipitated in the reaction mixture and collected by simple filtration. Otherwise, evaporation of the solvent gave the crude product which was purified by recrystallization in CH_2Cl_2.

Characterization data for selected compounds

2-(1-(2-oxopyrrolidin-1-yl)ethylamino)benzoic acid (**3ea**); White solid; m.p. 153–155°C; IR (KBr): *v* 3328, 1676, 1632, 1581, 1519, 754 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.52 (d, J = 6.4 Hz, 3H), 1.91–1.99 (m, 2H), 2.44–2.50 (m, 2H), 3.17–3.25 (m, 1H), 3.32–3.41 (m, 1H), 5.83 (q, J = 6.5 Hz, 1H), 6.70–6.75 (m, 1H), 6.82 (d, J = 8.5 Hz, 1H), 7.40–7.45 (m, 1H), 7.99–8.04 (m, 2H), 11.6 (brs, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.3, 18.8, 31.2, 40.4, 55.7, 109.3, 112.5, 116.0, 131.9, 135.4, 148.6, 172.4, 174.7 ppm; Anal. Calcd. (%) for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28; found: C, 62.99; H, 6.38; N, 11.08.

2-(1-(2-oxoazepan-1-yl)ethylamino)benzoic acid (**3eb**); White solid; m.p. 98–100°C; IR (KBr): *v* 2400–3600 (OH), 3317(NH), 1683, 1609, 1579, 760 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.22–1.27 (m, 1H), 1.44 (d, J = 6.3 Hz, 3H), 1.53–1.71 (m, 5H), 2.52–2.64 (m, 2H), 3.19–3.33

(m, 2H), 6.23–6.28 (m, 1H), 6.68–6.73 (m, 1H), 6.76 (d, *J* = 8.5 Hz, 1H), 7.39–7.45 (m, 1H), 7.99 (d, *J* = 7.9 Hz, 1H), 8.09 (d, *J* = 6.7 Hz, 1H) ppm, -OH not observed; ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.6, 23.3, 28.8, 30.0, 37.7, 41.3, 58.1, 109.6, 113.3, 116.3, 132.3, 135.7, 149.2, 172.8, 176.4 ppm; Anal. Calcd. (%) for $C_{15}H_{20}N_2O_3$: C, 65.20; H, 7.30; N, 10.14; found: C, 65.40; H, 7.19; N, 9.95.

1-(1-(naphthalen-2-ylamino)ethyl)pyrrolidin-2-one (**3na**); White solid; m.p. 149–151°C; IR (KBr) ν 3310, 2970, 1652, 1593, 1520, 1480, 810 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47 (d, *J* = 6.4 Hz, 3H), 1.79–1.86 (m, 2H), 2.35–2.42 (m, 2H), 3.12–3.19 (m, 1H), 3.26–3.33 (m, 1H), 4.29 (brs, 1H, NH), 5.81–5.85 (m, 1H), 6.89–6.93 (m, 2H), 7.20–7.27 (m, 1H), 7.34–7.39 (m, 1H), 7.63–7.69 (m, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.6, 19.2, 31.6, 40.7, 56.9, 106.1, 117.1, 122.4, 126.2, 126.3, 127.4, 127.7, 128.9, 134.9, 142.5, 174.8 ppm; Anal. Calcd. (%) for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.01; found: C, 75.66; H, 7.14; N, 11.20.

N-(4-(1-(2-oxopyrrolidin-1-yl)ethylamino)phenylsulfonyl)benzamide (**4a**); White solid; m.p. 193–196°C; IR (KBr): *ν* 3363, 1680, 1646, 1599, 825, 713 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.34 (d, *J* = 6.4 Hz, 3H), 1.84–1.86 (m, 2H), 2.20–2.26 (m, 2H), 3.02–3.08 (m, 1H), 3.27–3.38 (m, 1H), 5.47 (brs, 1H), 6.68 (d, *J* = 8.9 Hz, 2H), 7.20 (d, *J* = 7.4 Hz, 1H), 7.43–7.48 (m, 2H), 7.56–7.57 (m, 1H), 7.67 (d, *J* = 8.8 Hz, 2H), 7.82–7.85 (m, 2H)), 12.19 (brs, 1H) ppm; ^{13}C NMR (75MHz, DMSO-d_6) δ 17.2, 18.5, 30.9, 40.3, 55.6, 111.5, 125.6, 128.3, 128.5, 129.9, 131.7, 133.0, 150.7, 165.1, 173.7 ppm; Anal. Calcd. (%) for $C_{19}H_{21}N_3O_4S$: C, 58.90; H, 5.46; N, 10.85; found: C, 58.72; H, 5.33; N, 10.58.

4-(1-(2-oxopyrrolidin-1-yl)ethylamino)-N-(thiazol-2-yl)benzenesulfonamide (**4b**); White solid; m.p. 187–188°C; IR (KBr): *ν* 3351 (NH), 1681 (C = O), 1596, 1568, 931 cm^{-1}; ^{1}H

NMR (300 MHz, DMSO-d_6) δ 1.32 (d, J = 6.3 Hz, 3H), 1.73–1.87 (m, 2H), 2.19–2.24 (m, 2H), 2.96–3.02 (m, 1H), 3.23–3.32 (m, 1H), 5.43 (brs, 1H), 6.60 (d, J = 8.6 Hz, 2H), 6.73 (d, J = 5.5 Hz, 1H), 6.90 (d, J = 7.5 Hz, 1H), 7.18 (d, J = 4.6 Hz, 1H), 7.47 (d, J = 8.5 Hz, 2H), 12.45 (brs, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 17.3, 18.5, 30.9, 40.2, 55.6, 107.6, 111.6, 124.1, 127.5, 129.6, 149.3, 168.2, 173.6 ppm; Anal. Calcd. (%) for $C_{15}H_{18}N_4O_3S_2$: C, 49.16; H, 4.95; N, 15.29; found: C, 48.88; H, 4.81; N, 15.05.

Acknowledgment

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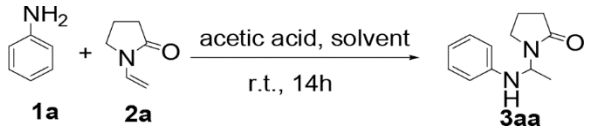
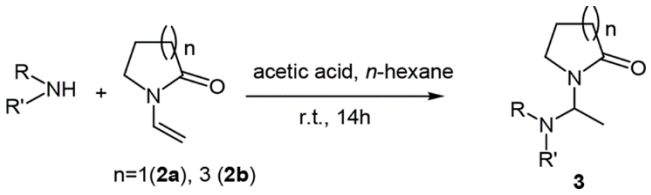
Table 1. Solvent effect on the Markovnikov addition reaction of aniline to *N*-vinylpyrrolidone.

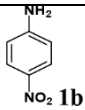
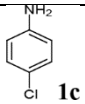
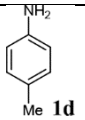
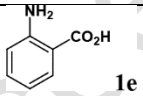
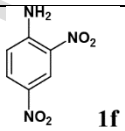
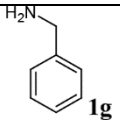


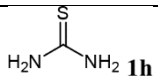
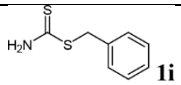
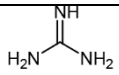
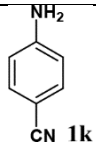
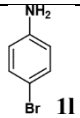
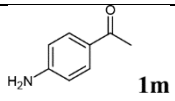
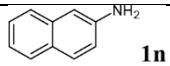
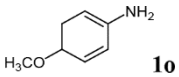
Solvent	THF	H_2O	CH_2Cl_2	Toluene	CH_3OH	*n*-hexane	ethylacetate	CH_3CN
Yield (%)[a,b]	65	65, 49[c], 34[d]	88	65	78	98	83	49

[a]Isolated yield. [b]Reaction condition: aniline (1 mmol), *N*-vinylpyrrolidone (1.2 mmol), solvent (3mL), acetic acid (1 equiv.), rt and 14h. [c]2 equiv. of acetic acid was applied. [d]0.5 equiv. of acetic acid was used.

Table 2. Diversity in the synthesis of aminals from amines and tertiary enamides

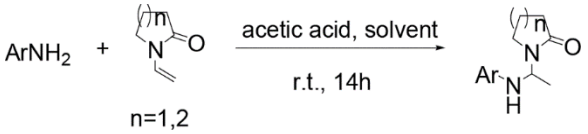


Entry	Amine	Enamide	Product	Yield (%)[a]
1	 **1a**	**2a**	**3aa**	98
2		**2b**	**3ab**	quant.
3	 **1b**	**2a**	**3ba**	quant.
4		**2b**	**3bb**	quant.
5	 **1c**	**2a**	**3ca**	quant.
6		**2b**	**3cb**	quant.
7	 **1d**	**2a**	**3da**	47
8		**2b**	**3db**	quant.
9	 **1e**	**2a**	**3ea**	quant.
10		**2b**	**3eb**	quant.
11	 **1f**	**2a**	–	NR[b]
12	 **1g**	**2a**	–	NR

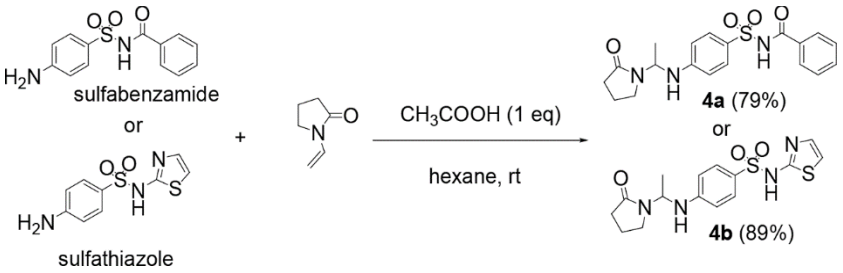
13	 **1h**	**2a**	–	NR
14	 **1i**	**2a**	–	NR
15	 **1j**	**2a**	–	NR
16	 **1k**	**2b**	**3kb**	52
17 18	 **1l**	**2a** **2b**	**3la** **3lb**	quant. quant.
19 20	 **1m**	**2a** **2b**	**3ma** **3mb**	60 75
21 22	 **1n**  **1o**	**2a** **2a**	**3na** **3oa**	53 50

[a]Isolated yield. [b]NR: No reaction.

Scheme 1. Synthesis of protected aminals from enamides



Scheme 2. Synthesis of aminals from sulfa drugs



Scheme 3. A tentative mechanism for the synthesis of aminals