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An effective aza-Michael addition of aromatic amines to electron-deficient alkenes in alkaline Al_2O_3

Xin Ai, Xin Wang *,†, Jin-ming Liu, Ze-mei Ge, Tie-ming Cheng, Run-tao Li *,†

State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences, Peking University, Beijing 100191, PR China

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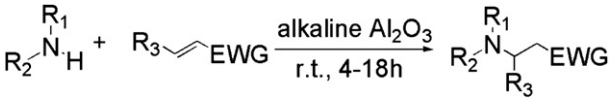
ABSTRACT

Aza-Michael addition of aromatic or aliphatic amines with various electron-deficient alkenes was performed using alkaline Al_2O_3 as solid media at room temperature afforded the corresponding Michael addition products in good to excellent yields. The alkaline Al_2O_3 can be easily recovered and reused.

1. Introduction

Owing to their wide range of biological activities[1] and pharmacological properties,[2] the synthesis of β-amino carbonyl compounds has become a field of increasing interest in organic synthesis during the past few decades.[3] The approach based on conjugate addition of amines to α, β-unsaturated carbonyl compounds (aza-Michael addition) is one of the simplest and most effective methods for preparing β-amino carbonyl compounds. In recent years, a number of catalysts such as SmI_2,[4] $Cu(OTf)_2$,[5] $Bi(NO_3)$,[6] $Bi(OTf)_2$,[7] $LiClO_4$,[8] $FeCl_3 \cdot 6H_2O$,[9] TMSCl,[10] boric acid[11] and clay[12] have been developed for this reaction. However, most of these catalytic systems are restricted to only aliphatic amines since aromatic amines are poor nucleophiles.[13] Therefore, the aza-Michael addition of aromatic amines encountered a big challenge until the introduction of aqueous media with promoting agents,[14] but the use of expensive and/or toxic catalysts, harsh reaction conditions limited their application in organic synthesis. As a consequence, several solvent-free or catalyst-free reaction conditions[15] have been developed. But some methods still have the drawbacks of low yields or finite scope of substrates. Hence, the requirement of developing new aza-Michael addition with a broad scope of substrates and mild reaction condition remains. In this paper, we report a simple and effective procedure for aza-Michael addition of aromatic and aliphatic amines to electron-deficient alkenes in alkaline Al_2O_3 at room temperature (Scheme 1).



Scheme 1. Aza-Michael addition of aromatic and aliphatic amines to electron-deficient alkenes in alkaline Al_2O_3.

2. Results and discussion

Previously, we have developed an effective methodology for the preparation of dithiocarbamic acid esters from Michael addition of electron-deficient alkenes with aromatic amines and CS_2 in alkaline Al_2O_3 as solid media.[16] During the course of investigating above reaction, we noticed that aniline could react with acrylonitrile directly to produce 3-(phenylamino) propanenitrile in alkaline Al_2O_3. This unusual finding aroused our interest to explore the possibility for aza-Michael addition of aromatic amines to electron-deficient alkenes in solid media.

In this connection, our first experiments were performed by reacting aniline and acrylonitrile in different solid media. As presented in Table 1, among the four screened solid media, namely silica gel, bentonite, Celite and alkaline Al_2O_3, alkaline Al_2O_3 was most effective for this reaction. Optimization for using amount of the alkaline Al_2O_3 revealed that the best yield was obtained when 1 g alkaline Al_2O_3 was used under the experimental scale.

* Corresponding authors. Tel.: +86 10 82 801 504; fax: +86 10 82 716 956; e-mail addresses: xinwang@bjmu.edu.cn (X. Wang), lirt@bjmu.edu.cn (R.-tao Li).
† Present address: No.38 Xueyuan Road, Haidian District, Beijing100191, PR China

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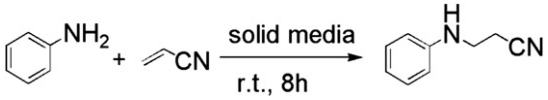
Table 1
Aza-Michael addition of aniline to acrylonitrile under different reaction conditions[a]



Entry	Solid media	Solid media amount (g)	Yield[b] (%)
1	Silica gel	1	Trace
2	Diatomite	1	23
3	Bentonite	1	54
4	Alkaline Al_2O_3	0	0
5	Alkaline Al_2O_3	0.5	82
6	Alkaline Al_2O_3	0.75	85
7	Alkaline Al_2O_3	1	98
8	Alkaline Al_2O_3	1.5	95

[a] The reaction was conducted with aniline (1 mmol), acrylonitrile (1.5 mmol) in solid media at room temperature.
[b] Isolated yields.

Subsequently, the structurally diverse aromatic amines were chosen to react with acylonitrile under optimized conditions in order to examine the versatility of the protocol and the results are summarized in Table 2. All examined aryl amines could react with acrylonitrile successfully to give corresponding aza-Michael addition products in moderate to excellent yields. Anilines bearing *para*- or *meta*-electron donating substitutions (entries 2, 3, 5) showed higher reactivity than their *ortho*-substituted analogues (entries 4, 6) because the latter have higher steric hindrance. To our pleasure, high yields could be provided in the cases of aniline containing electron-withdrawing groups (entries 7–9), which is reluctant to undergo Michael addition reaction according to previous literatures.[17] It is noticeable that even 3-nitroaniline, which has a strong electron-withdrawing group, still afforded the expected compound in 46% yield (entry 10). Meanwhile, using α-naphthylamine as nucleophile, moderate yield was achieved (entry 11). Furthermore, we applied the aza-Michael addition reaction to aryl diamine since substituted diamines were an important class of compounds for the preparation of hybrid materials[18] and functional nano-structured materials (entries 12, 13).[19] The results demonstrated that mono- or bis aza-Michael addition products of diamine could be acquired selectively through adjusting the relative mole ratio of the reactants.

To determine the adaptability of this protocol, some examples of aliphatic amines were investigated and satisfactory results were also obtained (Table 2, entries 14–20). In the cases of conventional aza-Michael addition, primary amine suffered from over-alkylation produced a low yield of the mono- or di-substituted products.[20] Whereas, in our cases, the ratios of mono- or di-substituted products were controllable by adding different proportions of acrylonitrile and afforded satisfactory yields (entries 14–17). In addition, *N*-hetero-aromatic amines were also effective and gave desired adducts in 94–96% yields (entries 21–23).

At last, we studied the reactions of aniline with different electron-deficient alkenes under our reaction conditions to test the generality of Michael acceptors. The three chosen Michael acceptors afforded the mono aza-Michael products in comparable yields (entries 24–26).

It is noteworthy that all cases were carried out just by mixing all reactants together and stirring at room temperature for 4–18 h. The products can be isolated from the reaction system by simply washing with ethyl acetate, and the alkaline Al_2O_3 can be easily recovered and reused for at least three times without any significant loss of activity. Pure products could be readily obtained by recrystallization from petroleum ether/ethyl acetate in most cases.

3. Conclusion

In conclusion, we have developed an effective aza-Michael addition of aromatic or aliphatic amines (primary or secondary) to electron-deficient alkenes in alkaline Al_2O_3. The advantages of this procedure include the wide scope of reaction substrates, the green and reused solid reaction media, high yields and simple work-up process. These remarkable advantages will make this approach suitable not only for laboratory scale research but also for industrial applications.

4. Experimental

4.1. General experimental

Melting point data were recorded on an X-4 micro-melting point instrument; NMR spectra were recorded on a Bruker ACF 300. Column chromatography was performed on silica gel, Merck grade 60. Alkaline Al_2O_3 and other chemicals were purchased from LANYI.

4.2. General procedure for the aza-Michael reaction

A mixture of amine (1 mmol), alkene (1.5 mmol) and alkaline Al_2O_3 (1 g) was stirred at room temperature for the indicated time in Table 2 (monitored by TLC). Then, the solid mixture was washed with ethyl acetate (10 mL) and the crude product was obtained after removing off the ethyl acetate from washing solution. Further purification was carried out by recrystallization from ethyl acetate/petroleum ether or short column chromatography on silica gel (ethyl acetate/petroleum ether=1:6). The recovered alkaline Al_2O_3 could be reused.

4.2.1. 3-(Phenylamino)propanenitrile (Table 2, entry 1). Yellow crystal; mp: 51–52 °C (lit.[21] 51.5 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.57 (t, 2H, J=2.2 Hz), 3.46 (dd, 2H, J=2.0, 1.9 Hz), 3.99 (s, 1H), 6.58–7.22 (m, 5H). NMR data were identical with those described in the literature.[21]

4.2.2. 3-(p-Toluidino)propanenitrile (Table 2, entry 2). Yellow crystal; mp: 102–103 °C (lit.[22] 103–104 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.25 (s, 3H), 2.63 (t, 2H, J=2.1 Hz), 3.51 (t, 2H, J=2.1 Hz), 3.84 (s, 1H), 6.56 (d, 2H, J=2.8 Hz), 7.03 (d, 2H, J=2.7 Hz). NMR data were identical with those described in the literature.[22]

4.2.3. 3-(m-Toluidino)propanenitrile (Table 2, entry 3). Yellow crystal; mp: 50–51 °C (lit.[23] 49.5–50.5 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.29 (s, 3H), 2.63 (t, 2H, J=2.2 Hz), 3.51 (dd, 2H, J=2.2, 2.1 Hz), 3.92 (s, 1H), 6.43 (d, 2H, J=2.2 Hz), 6.60 (d, 1H, J=2.1 Hz), 7.10 (t, 1H, J=2.2 Hz). NMR data were identical with those described in the literature.[23]

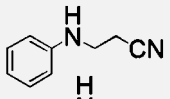
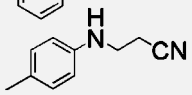
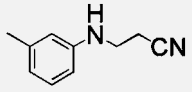
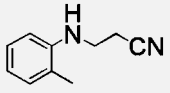
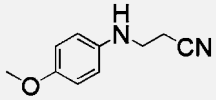
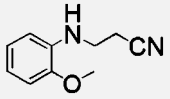
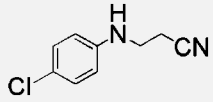
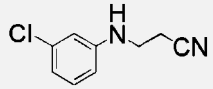
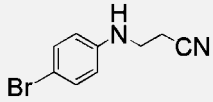
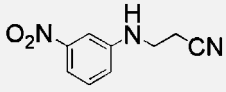
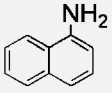
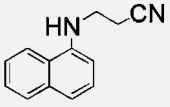
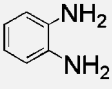
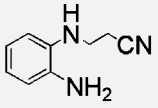
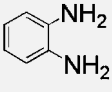
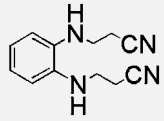
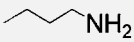
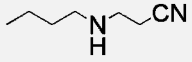
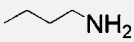
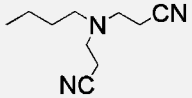
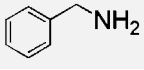
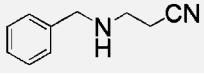
4.2.4. 3-(o-Toluidino)propanenitrile (Table 2, entry 4). Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.16 (s, 3H), 2.07 (t, 2H, J=2.2 Hz), 3.57 (dd, 2H, J=2.2, 2.1 Hz), 3.85 (s, 1H), 6.55–7.24 (m, 5H). NMR data were identical with those described in the literature.[23]

4.2.5. 3-(4-Methoxyphenylamino)propanenitrile (Table 2, entry 5). Yellow crystal; mp: 63–64 °C (lit.[23] 62–64 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.52 (t, 4H, J=2.2 Hz), 3.59 (t, 4H, J=2.2 Hz), 3.79 (s, 3H), 6.81–6.91 (m, 5H). NMR data were identical with those described in the literature.[23]

4.2.6. 3-(2-Methoxyphenylamino)propanenitrile (Table 2, entry 6). Yellow crystal; mp: 70–71 °C (lit.[24] 70–71 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.63 (t, 2H, J=2.2 Hz), 3.53 (dd, 2H, J=2.2, 2.1 Hz), 3.84 (s, 3H), 4.55 (s, 1H), 6.55–6.90 (m, 5H).

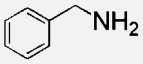
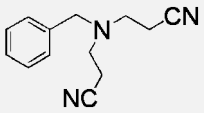
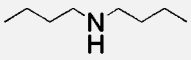
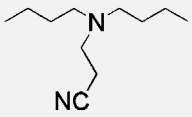
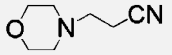
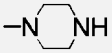
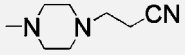
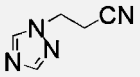
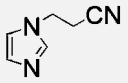
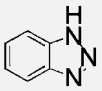
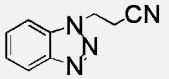
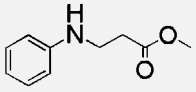
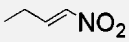
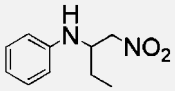
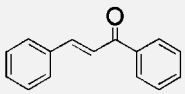
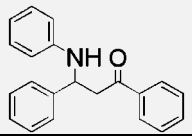
4.2.7. 3-(4-Chlorophenylamino)propanenitrile (Table 2, entry 7). Yellow crystal; mp: 75–76 °C (lit.[23] 75–76 °C); ^{1}H NMR (300 MHz,

Table 2
Aza-Michael addition of diverse nitrogen nucleophiles with Michael acceptors in alkaline Al_2O_3[a]

Entry	Nucleophile	Acceptor	Product	Time (h)	Yield[b] (%)
1	$PhNH_2$			8	98
2	*p*-CH_3PhNH_2			8	98
3	*m*-CH_3PhNH_2			8	95
4	*o*-CH_3PhNH_2			8	75
5	*p*-CH_3OPhNH_2			8	98
6	*o*-CH_3OPhNH_2			8	83
7	*p*-$ClPhNH_2$			8	88
8	*m*-$ClPhNH_2$			8	84
9	*p*-$BrPhNH_2$			8	86
10	*m*-NO_2PhNH_2			8	46
11				8	75
12				8	53
13[c]				18	76
14				4	74
15[c]				4	90
16				4	80

(*continued on next page*)

Table 2 (*continued*)

Entry	Nucleophile	Acceptor	Product	Time (h)	Yield[b] (%)
17[c]				4	88
18				4	98
19				4	95
20				4	96
21				8	95
22				8	96
23				8	94
24	$PhNH_2$			8	63
25	$PhNH_2$			8	64
26	$PhNH_2$			8	84

[a] Unless specified, the reaction was carried out with amines (1 mmol) and Michael acceptors (1.5 mmol) in the presence of alkaline Al_2O_3 (1 g).
[b] Isolated yields.
[c] The amount of acrylonitrile was twice as much as that used in the corresponding mono-substituted cases.

$CDCl_3$) δ 2.64 (t, 2H, J=2.2 Hz), 3.50 (t, 2H, J=2.2 Hz), 4.00 (s, 1H), 6.53–7.18 (m, 5H). NMR data were identical with those described in the literature.[23]

4.2.8. 3-(3-Chlorophenylamino)propanenitrile (Table 2, entry 8). Yellow crystal; mp: 46–47 °C (lit.[21] 44–47 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.64 (t, 2H, J=2.2 Hz), 3.50 (t, 2H, J=2.2 Hz), 4.00 (s, 1H), 6.53–7.18 (m, 5H).

4.2.9. 3-(4-Bromophenylamino)propanenitrile (Table 2, entry 9). Yellow crystal; mp: 96.5 °C (lit.[25] 96.5–97.5 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.64 (t, 2H, J=2.2 Hz), 3.50 (s, 2H), 4.01 (s, 1H), 6.49–7.32 (m, 5H).

4.2.10. 3-(3-Nitrophenylamino)propanenitrile (Table 2, entry 10). Yellow crystal; mp: 97–98 °C (lit.[25] 95–96 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.71 (t, 2H, J=2.2 Hz), 3.59 (t, 2H, J=2.2 Hz), 4.38 (s, 1H), 6.90–7.92 (m, 5H).

4.2.11. 3-(Naphthalen-2-ylamino)propanenitrile (Table 2, entry 11). Pink powder; mp: 70–71 °C (lit.[26] 69–70 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.65 (t, 2H, J=2.2 Hz), 3.58 (t, 2H, J=2.2 Hz), 4.59 (s, 1H), 6.51–7.80 (m, 5H).

4.2.12. 3-(2-Aminophenylamino)propanenitrile (Table 2, entry 12). Red crystal; mp: 117–119 °C (lit.[27] 116–118 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.66 (t, 2H, J=2.2 Hz), 3.48 (t, 2H, J=2.2 Hz), 6.63–6.85 (m, 4H).

4.2.13. N,N′-o-Phenylene-di-alanine dinitrile (Table 2, entry 13). Dark red crystal; mp: 117–118 °C (lit.[28] 116–118 °C); ^{1}H NMR

(300 MHz, $CDCl_3$) δ 2.66 (t, 4H, J=2.2 Hz), 3.46 (t, 4H, J=2.2 Hz), 6.70–6.89 (m, 4H).

4.2.14. 3-(Butylamino)propanenitrile (Table 2, entry 14). Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, 3H, J=2.4 Hz), 1.31–1.53 (m, 4H), 2.54 (t, 2H, J=2.2 Hz), 2.64 (t, 2H, J=2.2 Hz), 2.94 (t, 2H, J=2.2 Hz). NMR data were identical with those described in the literature.[29]

4.2.15. 3,3′-Butylimino-di-propionitrile (Table 2, entry 15). White oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.83 (t, 2H, J=2.2 Hz), 4.27 (t, 2H, J=2.2 Hz), 7.03 (s, 1H), 7.12 (s, 1H), 7.57 (s, 1H).

4.2.16. 3-(Benzylamino)propanenitrile (Table 2, entry 16). Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.52 (t, 2H, J=2.2 Hz), 2.83 (t, 2H, J=2.2 Hz), 3.83 (s, 2H), 7.26–7.34 (m, 5H). NMR data were identical with those described in the literature.[22]

4.2.17. 3,3′-[(Phenylmethyl)imino]bis(propanenitrile) (Table 2, entry 17). Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.42 (t, 2H, J=2.3 Hz), 2.84 (t, 2H, J=2.3 Hz), 3.67 (s, 2H), 7.26–7.34 (m, 5H). NMR data were identical with those described in the literature.[31]

4.2.18. 3-(Dibutylamino)propanenitrile (Table 2, entry 18). Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, 6H, J=2.3 Hz), 1.26–1.46 (m, 8H), 2.39–2.45 (m, 6H), 2.77 (t, 2H, J=2.3 Hz). NMR data were identical with those described in the literature.[29]

4.2.19. 3-Morpholinopropanenitrile (Table 2, entry 19). Yellow oil; mp: 128–129 °C (lit.[30] 128 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.50–2.55 (m, 6H), 2.65–2.70 (m, 2H), 3.69–3.72 (m, 4H). NMR data were identical with those described in the literature.[30]

4.2.20. 3-(4-Methylpiperazin-1-yl)propanenitrile (Table 2, entry 20). White crystal; mp: 97–98 °C (lit.[32] 96–100 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.26 (t, 3H, J=2.7 Hz), 2.48 (s, 8H, J=2.2 Hz), 2.67 (s, 2H), 8.22 (s, 1H). NMR data were identical with those described in the literature.[32]

4.2.21. 3-(1H-1,2,4-Triazol-1-yl)propanenitrile (Table 2, entry 21). White oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.01 (t, 2H, J=2.2 Hz), 4.48 (t, 2H, J=2.2 Hz), 8.02 (s, 1H), 8.22 (s, 1H). NMR data were identical with those described in the literature.[33]

4.2.22. 3-(1H-Imidazol-1-yl)propanenitrile (Table 2, entry 22). White crystal; mp: 35–36 °C (lit.[34] 33–35 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.83 (t, 2H, J=2.2 Hz), 4.27 (t, 2H, J=2. 2 Hz), 7.03 (s, 1H), 7.12 (s, 1H), 7.57 (s, 1H). NMR data were identical with those described in the literature.[34]

4.2.23. 3-(1H-Benzo[d][1,2,3]triazol-1-yl)propanenitrile (Table 2, entry 23). White crystal; mp: 83–84 °C (lit.[35] 83–85 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.15 (t, 2H, J=2.2 Hz), 4.94 (t, 2H, J=2.2 Hz), 7.41–8.12 (m, 5H). NMR data were identical with those described in the literature.[35]

4.2.24. Methyl 3-(phenylamino)propanoate (Table 2, entry 24). White crystal; mp: 49–50 °C (lit.[36] 50 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.57 (t, 2H, J=2.2 Hz), 3.46 (dd, 2H, J=2.0, 1.9 Hz), 3.70 (s, 3H), 3.99 (s, 1H), 6.58–7.22 (m, 5H). NMR data were identical with those described in the literature.[36]

4.2.25. N-(1-Nitrobutan-2-yl)benzenamine (Table 2, entry 25). Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (t, 2H, J=2.4 Hz), 1.56–1.80 (m, 2H), 3.67 (d, 1H, J=3.0 Hz), 4.01 (d, 1H, J=1.8 Hz), 4.41–4.59 (m, 2H), 6.66–7.26 (m, 5H). NMR data were identical with those described in the literature.[37]

4.2.26. 1,3-Diphenyl-3-(phenylamino)propan-1-one (Table 2, entry 26). Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.38–3.55 (m, 2H), 4.55 (s, 1H), 5.00 (s, 1H), 6.55–7.92 (m, 15H). NMR data were identical with those described in the literature.[38]

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Supplementary data

The original data of ^{1}H NMR of all products are supplied. The supplementary data files are to be used as an aid for the referring of the paper only. Supplementary data for this article can be found in the online version, at doi:10.1016/j.tet.2010.05.054. These data include MOL files and InChIKeys of the most important compounds described in this article.

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