Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Efficient Method for the Synthesis of Michael Adducts Using Kaolin Preloaded with KOH

G. Srihari [a] & M. Marthanda Murthy [a]
[a] Organic Chemistry Division II, Indian Institute of Chemical Technology , Hyderabad, India
Published online: 29 Jan 2009.

To cite this article: G. Srihari & M. Marthanda Murthy (2009) Efficient Method for the Synthesis of Michael Adducts Using Kaolin Preloaded with KOH, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 39:5, 896-906, DOI: 10.1080/00397910802439191

To link to this article: http://dx.doi.org/10.1080/00397910802439191

Synthetic Communications®, 39: 896–906, 2009

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910802439191

Taylor & Francis
Taylor & Francis Group

Efficient Method for the Synthesis of Michael Adducts Using Kaolin Preloaded with KOH

G. Srihari and M. Marthanda Murthy
Organic Chemistry Division II, Indian Institute of Chemical Technology, Hyderabad, India

Abstract: Michael addition of various active methylene compounds to β-nitrostyrenes is efficiently catalyzed by using Kaolin preloaded with KOH in acetonitrile at room temperature with moderate to good yields.

Keywords: Active methylene compounds, kaolin/KOH, Michael reaction, nitrostyrenes

INTRODUCTION

Michael addition products have a wide range of applications in synthetic organic chemistry. In particular, Michael addition of active methylene compounds to nitro styrenes afforded nitro alkanes. The nitro group is converting into different functionalities[1] such as Nef reaction, Meyer reaction, reduction to amino group, and conversion into the nitrile oxide for 1,3-dipolar cycloaddition reactions. These nitrogen-containing compounds are much more useful in pharmaceutical and agrochemical sectors.[2] The Michael reactions have numerous applications in the elegant synthesis of fine chemicals and are classically catalyzed by bases or suitable combinations of amines and carboxylic or Lewis acids under homogeneous conditions. The employment of these bases in the reactions encounters environmental problems. There has been increasing attention on the design and use of environmentally compatible solid base catalysts.[3]

Received June 23, 2008.
Address correspondence to M. Marthanda Murthy, Organic Chemistry Division II, IICT, Tarnaka 500007, India. E-mail: marthanda52@yahoo.com

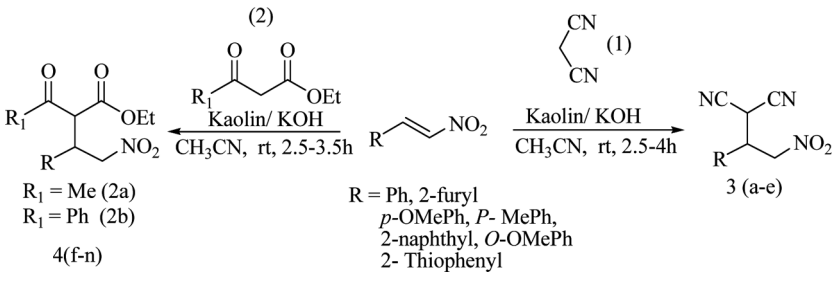
Different groups reported the Michael addition under homogeneous conditions, like AgoTf-PPh_3 complex in water[4] and polymer-anchored metal catalyst in different solvents,[5] and workup procedures are typical in homogeneous medium. Nowadays, heterogeneous catalyst plays an important role in various organic transformations. Recently the Michael reaction was reported by using acidic Al_2O_3[6] and different chiral catalysts.[7]

There are several advantages of engaging a supported reagent in organic synthesis. They offer remarkable ease of handling and use. Alumina, silica, and aluminosilicates (clays and zeolites) are some of the most widely employed supports, where surface hydroxyl groups play a major role in these reactions. Surface acidity of clays can be reduced substantially by introducing inorganic bases such as NaOH and KOH. These modified clays are highly basic and can be employed for base-catalyzed reactions. Recent years have witnessed a phenomenal growth in the use of high-surface-area inorganic solids as reaction media for organic transformations.[8]

In our ongoing research on heterogeneous systems, we found that Kaolin preloaded with potassium hydroxide (KOH)[9] is an efficient catalyst for Michael reactions in acetonitrile. This method is very simple, efficient, and suitable for large-scale operations.

RESULTS AND DISCUSSIONS

In general, the reaction has been carried by taking the two components (nitrostyrenes and active methylene compound in acetonitrile) and adding a catalytic amount of Kaolin/KOH. The mixture was stirred at room temperature (Scheme 1), which afforded the corresponding Michael adducts in moderate to good yields.



Scheme 1. Synthesis of Michael adducts.

Entry a was taken as a representative example for comparing reaction rates in various solvents such as dichloromethane (DCM), acetonitrile (CH_3CN), *N,N*-dimethyl formamide (DMF), dimethylsulfoxide (DMSO), methanol (MeOH), and water. No product formation was observed in DCM, DMF, DMSO, and water even under reflux conditions. The reaction progressed smoothly in the case of methanol and acetonitrile, and better yields were observed in acetonitrile. After optimizing the condition, we next applied the generality of addition of various nitrostyrens to active methylene compounds and results obtained are listed in Table 1. The products obtained are diastereomers (1:1 mixture) in the case of ethyl acetoacetate and ethyl benzoylacetate, whereas in the case of malanonitrile the products are racemic.

We screened various nitrostyrenes with malanonitrile, ethyl acetoacetate, and ethyl benzoylacetate. Electron-donating groups on aryl nitrostyrenes take longer than unsubstituted nitrostyrenes. The products were identified by spectroscopy [^{1}H NMR, infrared (IR), and mass spectroscopy (MS)] or otherwise compared with known compounds. The procedure described in this article was found to be more effective than those described in earlier reports.

CONCLUSION

In conclusion, we have developed a simple, convenient, and practical method for the synthesis of Michael adducts by using Kaolin preloaded with KOH.

EXPERIMENTAL

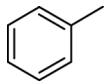
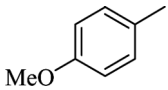
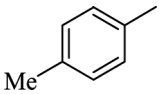
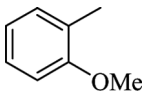
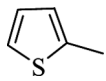
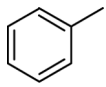
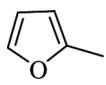
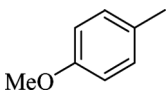
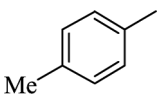
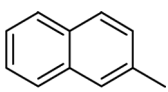
General Procedure for Synthesis of Michael Adducts

A mixture of nitro styrenes (1 mmol), active methylene compounds (1.2 mmol), and a catalytic amount of Kaolin/KOH taken in acetonitrile (2 mL) was stirred at room temperature for the appropriate time as mentioned in Table 1. The reaction was monitored by thin-layer chromatography (TLC). The product was filtered, and the crude product was purified by column chromatography.

General Procedure for the Preparation of Solid Support Preloaded with Base

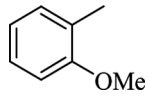
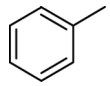
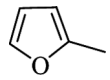
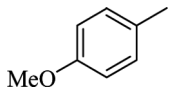
Kaolin clay (3 g) was added to 4 ml of 25% KOH solution, and the mixture was sonicated for a period of 4 h, then dried in a rotary evaporator

Table 1. Conjugate addition of active methylene compounds to nitrostyrenes

Entry	Nitro styrene R	Active methylene compound	Product[a]	Time (h)	Yield[b] (%)
a		1	3a	2.5	79
b		1	3b	4.0	82
c		1	3c	3.2	80
d		1	3d	3.8	80
e		1	3e	3.0	77
f		2a	4f	2.6	82
g		2a	4g	2.8	81
h		2a	4h	3.5	77
i		2a	4i	3.3	85
j		2a	4j	3.0	76

(*Continued*)

Table 1. Continued

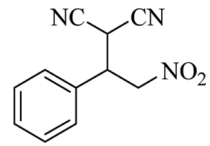
Entry	Nitro styrene R	Active methylene compound	Product[a]	Time (h)	Yield[b] (%)
k		2a	4k	3.2	68
l		2b	4l	2.0	73
m		2b	4m	2.5	71
n		2b	4n	3.0	70

[a]All products were characterized by IR, ^{1}H NMR, and mass spectroscopy.
[b]Unoptimized, isolated yields.

for several hours (obtaining solid support with suitable residual water). Residual traces of water were removed from the support by irradiating with microwaves for 15 min. The solid was ground to a powder. The solid support thus prepared contains about 6 mmol of KOH per gram.

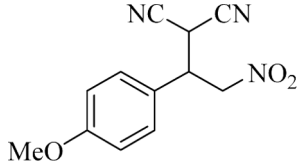
Spectral Data of Compounds

Compound **3a**



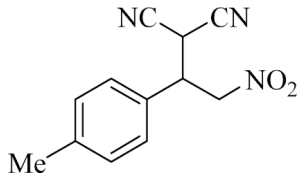
Viscous oil. IR (KBr): 2930, 2225, 1610, 1560, 1455; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.49$–7.30 (m, 5H), 4.98–4.88 (m, 2H), 4.40 (d, 1H), 4.10–4.02 (m, 1H); ESI-MS: 215 ($[M]^+$).

Compound **3b**



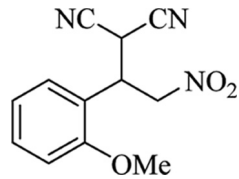
Viscous oil. IR (KBr): 2919, 2228, 1611, 1557, 1514, 1256, 1181; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.25$–6.90 (m, 4H), 4.95–4.75 (m, 2H), 4.35 (d, 1H), 4.05–3.98 (m, 1H), 3.82 (s, 3H); ESI-MS: 245 ($[M]^+$).

Compound **3c**



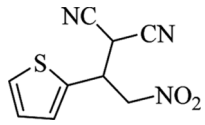
Solid. Mp 99–101 °C; IR (KBr): 2921, 2253, 1611, 1555, 1514, 1435; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.30$–7.20 (m, 4H), 5.01–4.80 (m, 2H), 4.38 (d, 1H), 4.05–3.95 (m, 1H), 2.40 (s, 3H); ESI-MS: 229 ($[M]^+$).

Compound **3d**



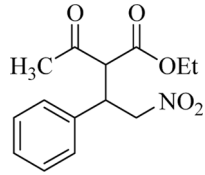
Solid. Mp 95–97 °C; IR (KBr): 2919, 2257, 1604, 1556, 1495, 1436, 1252; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.45$–7.40 (m, 1H), 7.28–7.20 (m, 1H), 7.09–6.95 (m, 2H); ESI-MS: 245 ($[M]^+$).

Compound **3e**



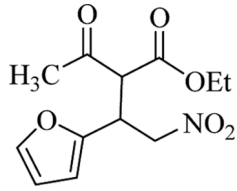
Solid. Mp 115–117 °C; IR (KBr): 2923, 2202, 1645, 1554, 1410, 1376; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.40$–7.01 (m, 3H), 4.95–480 (m, 2H), 4.55–4.40 (m, 2H); ESI-MS: 244 ($[M + Na]^+$).

Compound **4f**



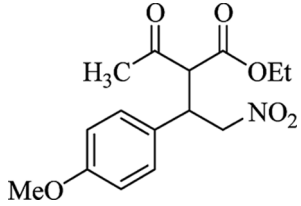
Solid. Mp 93–94 °C; IR (KBr): 2925, 1736, 1632, 1562, 1493, 1381; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.30$–7.20 (m, 3H), 7.18–7.12 (m, 2H), 4.78–4.68 (m, 2H), 4.25–4.09 (m, 2.5H), 3.90–4.01 (m, 1.5H), 2.30 (s, 1.5H), 2.04 (s, 1.5H), 1.28 (t, 1.5H), 1.01 (t, 1.5H); ESI-MS: 279 ($[M]^+$).

Compound **4g**



Viscous oil. IR (KBr): 2922, 1739, 1718, 1556, 1374; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.35$ (s, 1H), 6.28 (s, 1H), 6.18 (d, 1H), 4.81–4.68 (m, 2H), 4.38–4.02 (m, 4H), 2.30 (s, 1.5H), 2.15 (s, 1.5H), 1.28 (t, 1.5H), 1.18 (t, 1.5H); ESI-MS: 269 ($[M]^+$).

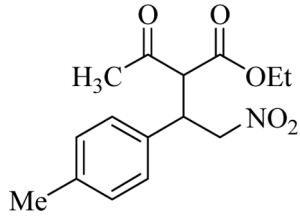
Compound **4h**



Viscous oil. IR (KBr): 2980, 1741, 1717, 1611, 1555, 1514; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.09$ (d, 2H), 6.78 (d, 2H), 4.77–4.63 (m, 2H),

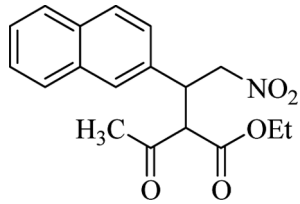
4.25–3.90 (m, 4H), 3.75 (s, 3H), 2.28 (s, 1.5H), 2.05 (s, 1.5H), 1.25 (t, 1.5H), 1.05 (t, 1.5H); ESI-MS: 309 ($[M]^+$).

Compound **4i**



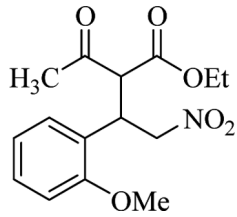
Viscous oil. IR (KBr): 2983, 1739, 1717, 1554, 1375; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.15$–7.02 (m, 4H), 4.76–4.64 (m, 2H), 4.25–3.95 (m, 4H), 2.32 (s, 3H), 2.26 (s, 1.5H), 2.02 (s, 1.5H), 1.25 (t, 1.5H), 1.05 (t, 1.5H); ESI-MS: 316 ($[M + Na]^+$).

Compound **4j**



Solid. Mp 107–108 °C; IR (KBr): 2924, 1738, 1561, 1375; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.85$–7.67 (m, 4H), 7.53–7.42 (m, 2H), 7.35–7.27 (m, 1H), 4.92–4.81 (m, 2H), 4.40–4.31 (m, 3H), 3.98–3.89 (m, 1H), 2.30 (s, 1.5H), 2.07 (s, 1.5H), 1.28 (t, 1.5H), 0.91 (t, 1.5H); ESI-MS: 352 ($[M + Na]^+$).

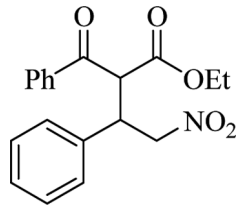
Compound **4k**



Viscous oil. IR (KBr): 2981, 1717, 1597, 1553; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.29$–7.19 (m, 1H), 7.15–7.01 (m, 1H), 6.91–6.84 (m, 2H),

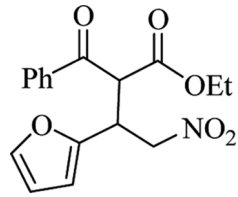
4.95– 4.69 (m, 2H), 4.35– 4.19 (m, 4H), 3.90 (s, 1.5H), 3.85 (s, 1.5H), 2.30 (s, 1.5H), 2.02 (s, 1.5H), 1.28 (t, 1.5H), 0.98 (t, 1.5H), ESI-MS: 309 ($[M]^+$).

Compound **4l**



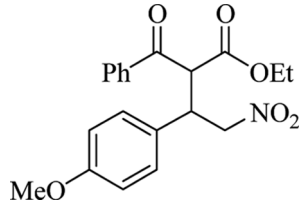
Solid. Mp 79–80 °C; IR (KBr): 2924, 1726, 1686, 1597, 1551; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 8.05$–7.89 (m, 2H), 7.61–7.45 (m, 4H), 7.31–7.18 (m, 4H), 4.95–4.88 (m, 2H), 4.76 (d, 1H), 4.50–4.38 (m, 1H), 4.20–4.06 (q, 1H), 3.90–3.79 (q, 1H), 1.21 (t, 1.5H), 0.92 (t, 1.5H); ESI-MS: 341 ($[M]^+$).

Compound **4m**



Viscous oil. IR (KBr): 2923, 1735, 1685, 1555; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 8.08$–7.95 (m, 2H), 7.65–7.35 (m, 4H), 6.30–6.09 (m, 2H), 5.05–4.85 (m, 2H), 4.80–4.75 (m, 1H), 4.60–4.48 (m, 1H), 4.20–4.11 (q, 1H), 4.08–3.95 (q, 1H), 1.18 (t, 1.5H), 1.07 (t, 1.5H); ESI-MS: 354 ($[M + Na]^+$).

Compound **4n**



Viscous oil. IR (KBr): 2924, 1735, 1684, 1611, 1553; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 8.07$–7.98 (m, 1H), 7.86–7.78 (m, 1H), 7.65–7.40 (m, 3H),

7.20–7.08 (m, 2H), 6.85–6.70 (m, 2H), 4.90–4.82 (m, 2H), 4.75–4.68 (m, 1H), 4.40–4.30 (m, 1H), 4.20– 4.10 (q, 1H), 3.95–3.82 (q, 1H), 3.75 (s, 1.5H), 3.68 (s, 1.5H), 1.19 (s, 1.5H), 0.92 (s, 1.5H); ESI-MS: 394 ($[M]^+$).

ACKNOWLEDGMENT

We thank Dr. J. S. Yadav (director) and Dr. V. V. N. Reddy (head of department) of the Indian Institute of Chemical Technology, Hyderabad, for constant encouragement and financial support.

REFERENCES

1. (a) Ballini, R.; Petrini, M. Recent synthetic developments in the nitro to carbonyl conversion. *Tetrahedron* **2004**, *60*, 1017; (b) Tamura, R.; Kamimura, A.; Ono, N. Displacement of aliphatic nitro groups by carbon and heteroatom nucleophiles. *Synthesis* **1991**, 423; (c) Poupart, M. A.; Fazal, G.; Goulet, S.; Mar, L. T. Solid phase synthesis of peptidyl trifluoromethyl ketone. *J. Org. Chem.* **1999**, *64*, 1356; d) Kamlet, M. J.; Kaplan, L. A.; Dacons, J. C. Reactions of polynitroalkanes with hot mineral acids. *J. Org. Chem.* **1961**, *26*, 4371; (e) Mukayama, T.; Hoshino, T. The Reactions of primary nitro paraffins with isocyanates. *J. Am. Chem. Soc.* **1960**, *82*, 5339.
2. (a) Barnes, D. M.; Ji, J. G.; Fickes, M. G.; Fitzgerald, M. A.; King, S. A.; Morton, H. E.; Plagge, F. A.; Preskill, M.; Wagaw, S. H.; Wittenberger, S. J.; Zhang, J. Development of a catalytic enantioselective conjugate addition of 1,3-dicarbonyl compounds to nitroalkenes for the synthesis of endothelin-A antagonist ABT-546: Scope, mechanism, and further application to the synthesis of the antidepressant rolipram. *J. Am. Chem. Soc.* **2002**, *124*, 13097; (b) Hoashi, Y.; Yabuta, T.; Takemoto, Y. Bifunctional thiourea-catalyzed enantioselective double Michael reaction of γ,δ-unsaturated β-ketoesters to nitroalkanes: Asymmetric synthesis of (−)-epibatidine. *Tetrahedron Lett.* **2004**, *45*, 9185.
3. Choudary, B. M.; Lakshmi Kantam, M.; Kavita, B.; Venkat Reddy, C.; Figueras, F. Catalytic C-C bond formation promototed by Mg-Al-O-tBu hydrotalcite. *Tetrahedron* **2000**, *56*, 9357.
4. Shirakava, S.; Kobayashi, S. Ag(I)-catalyzed Michael additions of β-ketoesters to nitroalkenes in water: Remarkable effect of water as a reaction medium on reaction rates. *Synlett* **2006**, 1410.
5. Fei, C. P.; Chan, T. H.; Chan, T. H. Michael reaction catalysed by polymer-anchored metal acetylacetonates. *Synthesis* **1982**, 467.
6. Ballini, R.; Maggi, R.; Palmieri, A.; Sartori, G. Acidic alumina as a useful heterogeneous catalyst in the Michael reaction of β-dicarbonyl derivatives with conjugated nitroalkenes. *Synthesis* **2007**, 3017.
7. (a) Chen, F.; Shao, C.; Wang, Q.; Gong, P.; Zhang, D.; Zhang, B.; Wang, R. An enantioselective Michael addition of malonate to nitroalkenes catalyzed by

low loading demethylquinine salts in water. *Tetrahedron Lett.* **2007**, *48*, 8456; (b) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. Enantio- and diastereoselective Michael reaction of 1,3-dicarbonyl compounds to nitroolefins catalyzed by a bifunctional thiourea. *J. Am. Chem. Soc.* **2005**, *127*, 119; (c) Kotrusz, P.; Toma, S.; Schmalz, H. G.; Adler, A. Michael additions of aldehydes and ketones to β-Nitrostyrenes in an ionic liquid. *Eur. J. Org. Chem.* **2004**, 1577.

8. Varma, R. S. Clay and clay-supported reagents in organic synthesis. *Tetrahedron* **2002**, *58*, 1235.
9. (a) Yu, H.; Koshima, H. A convenient method for asymmetric alkylation of glycine imine esters using solid supports. *Tetrahedron Lett.* **2003**, *44*, 9209; (b) Yu, H.; Takigawa, S.; Koshima, H. Asymmetric alkylation of glycineimine esters using solid supports preloaded with base. *Tetrahedron* **2004**, *60*, 8405.