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# A one-pot, three component synthesis of ketenimines under solvent-free conditions

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**Abstract:** A three-component, one-pot reaction between CH-acids, cyclohexyl isocyanide and dimethyl acetylenedicarboxylate yields stable ketenimines under solvent-free conditions in good yields.

**Keywords:** Ketenimines, MCRs, Isocyanides, DMAD, Solvent-free, CH-acids.

## Introduction

Multi-component reactions (MCRs) are special types of synthetically useful organic reaction in which three or more different starting materials react to a final product in a one-pot procedure [1]. MCRs are powerful tools in the modern drug discovery process and allow the fast, automated and high throughput generation of organic compounds [2].

In this paper we present a three-component reaction of cyclohexyl isocyanides **1**, dimethyl acetylenedicarboxylate **2** and CH-acids **3** yielding stable ketenimines **4a, b** in one-pot (Scheme **1**). Ketenimines play a role as discrete but transient intermediates in many interconversions, specially in elimination-addition processes and in the formation of heterocyclic systems [3-6]. They have also attracted interest as dehydrating agent for peptide synthesis, as complexing agents for transition metal ions, and as co-reagents for DMSO oxidation [7, 8].

In continuation of our interest in the application of MCRs in organic syntheses [9-14], we synthesized highly functionalized ketenimines via MCRs under solvent-free conditions. Solvent-free reactions have many advantages such as considering the green chemistry principles and decreasing byproduct formation and, hence, decreased waste [15].

The reactivity of nucleophilic carbenes such as isocyanides towards dimethyl acetylenedicarboxylate (DMAD) is well documented [16-18]. The reaction of isocyanides with carbon-carbon triple bonds occurs in a stepwise manner through a zwitterionic intermediate, the ultimate fate of which appears to be dictated by the nature of original triple-bonded substrate [19-24].

## Results and discussion

The reaction of cyclohexyl isocyanide **1** with electron deficient acetylenic ester **2** in the presence of strong CH-acids **3a, b** proceeded under solvent-free and was completed within 12-16h at room temperature.

The structure of compounds **4a, b** was deduced from their IR, $^1$H NMR, $^{13}$C NMR, mass spectral data and elemental analysis. The mass spectra of these compounds **4a, b** displayed molecular ion peaks at appropriate *m/e* values. The $^1$H NMR spectrum of compound **4a** exhibited a multiplet for the cyclohexyl ring (δ 1.22-1.58 ppm), two singlet for two methyl groups (δ 2.31 and 2.35 ppm), two singlet for the methoxy groups (δ 3.67 and 3.68 ppm), a multiplet for the N-CH cyclohexyl proton (δ 3.76 ppm), a singlet for

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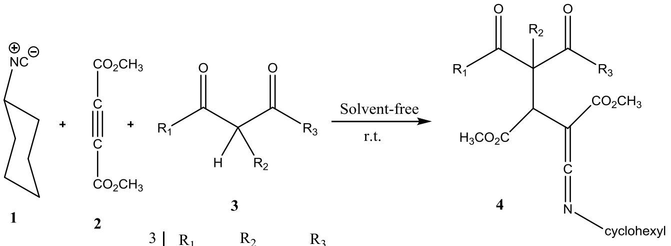
the methoxy groups (δ 3.82 ppm) and a singlet for $CHCO_2$ (δ 4.64 ppm).



1 2 3 4

| 3 | $R_1$ | $R_2$ | $R_3$ |
|---|---|---|---|
| a | $CH_3$ | $COOCH_3$ | $CH_3$ |
| b | $CF_3$ | H | SCH3 |

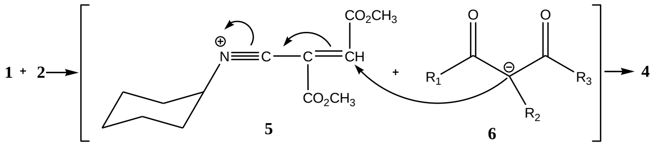
| 4 | Time(h) | %Yield |
|---|---|---|
| a | 12 | 88 |
| b | 16 | 80 |

**Scheme 1:** Synthesis of compounds **4a, b**.

The $^{13}C$ NMR spectrum of **4a** showed eighteen distinct resonances in agreement with proposed structure. The characteristic signals due to *C*=C=N and C=*C*=N groups were discernible at δ 55.1 and 192.4 ppm, respectively. The spiro carbon resonated at δ 79.3 ppm. Partial assignment of these resonances is given in the experimental data.

The structural assignment made on the basis of the $^1H$ and $^{13}C$ NMR spectra of compound **4a** was supported by measurement of its IR spectra. The IR spectra of **4a** showed strong absorptions at 2065 $cm^{-1}$ due to ketenimine group. The $^1H$ and $^{13}C$ NMR spectra of **4b** are similar to **4a** and the results are described in experimental section.

The plausible way of formation of the product is proposed in scheme **2**. It is reasonable to assume that compound **4** results from initial addition of cyclohexyl isocyanide and acetylenic ester [20, 25] and subsequent protonation of the 1:1 adduct by the CH-acid **3**. Then, the positively charged ion **5** is attacked by the base **6** to form ketenimine **4** (Scheme **2**).



5 6

**Scheme 2:** Proposed mechanism for the formation of compound **4**.

## Conclusion

In summary, we have reported that the reaction of cyclohexyl isocyanide with dimethyl acetylenedicarboxylate in the presence of CH-acids leads to the one-pot and simple synthesis of stable polyfunctionalized ketenimines under solvent-free conditions. The presented method has the advantage of being performed under neutral, solvent-free conditions and requires no activation or modification of the reagent.

## Experimental

### *General:*

Cyclohexyl isocyanide, dimethyl acetylenedicaboxylate, methyl 2-acetyl-3-oxobutanoate and methyl 4,4,4-trifluoro-3-oxobutanethioate were purchased from Fluka, Merk and Aldrich and used without further purification. Melting points and IR spectra were measured on an Electrothermal 9100 apparatus and a Shimadzu IR–470 spectrometer respectively. The $^1H$ and $^{13}C$ NMR spectra were recorded on a Bruker DRX–250 Avance instrument with $CDCl_3$ as solvent at 250.1 and 62.9 MHz, respectively. Mass spectra were recorded on a Shimadzu GC/MS QP 1100 EX mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyser.

### *General synthetic procedure (exemplified by* **4a***):*

Cyclohexyl isocyanide (0.13 g, 1.2 mmol) was slowly added dropwise to a magnetically stirred mixture of methyl 2-acetyl-3-oxobutanoate (1mmol) and DMAD (0.17 g, 1.2 mmol) in solvent-free conditions at room temperature. Then, after 12 hour, the solid product washed with mixture of cold diethyl ether and n-hexane with 1: 3 ratio (2×3 mL). The liquid phase was filtered off and residue recrystallized in diethyl ether.

### *Trimethyl 4-acetyl-1-(cyclohexylimino)-5-oxohex-1-ene-2,3,4-tricarboxylate* **(4a)**:

White powder, yield 88%, 0.36 g, mp 164-166 ºC; IR (KBr) ($\nu_{max}$, $cm^{-1}$): 2065 (C=C=N). $^1H$ NMR (250.1 MHz, $CDCl_3$): $\delta_H$ 1.22-1.58 (10H, m, $5CH_2$), 2.31 (3H, s, COMe), 2.35 (3H, s, COMe), 3.67 and 3.68 (6H, 2s, $2OCH_3$), 3.76 (1H, m, CHN), 3.82 (3H, s, $OCH_3$), 4.64 (1H, s, $CHCO_2$). $^{13}C$ NMR (62.9 MHz, $CDCl_3$): $\delta_C$ 23.9, 25.2 and 33.0 ($5CH_2$ of cyclohexyl), 26.0 (*C*HCO), 29.0 and 29.7 (2CO*C*$H_3$), 51.7 ($CO_2$*C*$H_3$), 52.7 and 53.0 ($2CO_2$*C*$H_3$), 55.1 (C=C), 60.3 (N-CH), 79.3 ($C_{Spiro}$), 163.9 (C=O), 171.2 and 171.3 (2C=O), 192.4 (C=N), 200.2 and 200.9 (2*C*OMe). MS, *m/e* (%) = 409 ($M^+$, 15), 326 (10), 293 (50), 221 (100), 176 (6), 83 (32), 59 (8); Anal. Calcd for $C_{20}H_{27}NO_8$ (409.43): C, 58.67; H, 6.65; N, 3.42%. Found: C, 58.80; H, 6.71; N, 3.51%.

*Dimethyl2-((cyclohexylimino)methylene)-3-(4,4,4-trifluoro-1-(methylthio)-1,3-dioxobutan-2-yl) succinate* **(4b)**:

Yellow powder, yield: 80%, 0.35 g, mp 138-141 ºC; IR (KBr) ($\nu_{max}$, cm$^{-1}$): 2130 (C=C=N). $^1$H NMR (250.1 MHz, $CDCl_3$): $\delta_H$ 1.21-1.71 (10H, m, $5CH_2$), 2.41 (3H, s, SMe), 3.38 (1H, d, $^3J_{HH}$ = 7.5 Hz, $CHCO_2$), 3.60-3.68 (1H, m, CHCS), 3.66 and 3.68 (6H, 2s, $2OCH_3$), 3.76 (1H, m, CHN). $^{13}$C NMR (62.9 MHz, $CDCl_3$): $\delta_C$ 20.89 (SMe), 24.2, 24.3 and 24.6 ($5CH_2$ of cyclohexyl), 32.6 (*C*$HCO_2$), 50.3 (*C*HCS), 51.1 and 52.7 ($2CO_2$*C*$H_3$), 56.7 (C=C), 70.3 (N-CH), 116.3 ($CF_3$), 168.5 and 170.9 (2*C*$O_2$Me), 189.6 (C=N), 197.6 (*C*$OCF_3$), 207.1 (CS). MS, *m/e* (%) = 438 ($M^+$+1, 12), 437 ($M^+$, 7), 390 (56), 378 (25), 83 (100) ; Anal. Calcd for $C_{18}H_{22}F_3NO_6S$ (437.4): C, 49.42; H, 5.07; N, 3.20 %. Found: C, 49.56; H, 5.11; N, 3.29 %.

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## References

[1] Domling, A.; Ugi, I. *Angew. Chem., Int. Ed. Eng.*, **2000**, *39*, 3168.
[2] Weber, L. *Curr. Med. Chem*. **2002**, *9*, 1241.
[3] Arrieta, A.; Cossio, F. P.; Lesea, B. *J. Org. Chem.*, **1999**, *64*, 1831.
[4] Aumann, R.; Jasper, B.; Lage, M.; Kerbs, B. *Organometallics*, **1994**, *13*, 3502.
[5] Getzmann, R.; Moller, M. H.; Rodewald, U.; Frohlich, R.; Grehl, M.; Wurthwein, E. U. *Tetrahedron*, **1995**, *51*, 3767.
*[6]* Coyl, J. D. *J. Chem. Soc. Perkin Trans.* 2, **1981**, 270.
[7] Barker, M. W.; McHenry, W. E. *The chemistry of ketenes, Allenes and Related Compounds*, Patai, S. (ed.), Wiley, Chichester, **1980**, pp. 702-720.
[8] Krow, G. R. *Angew. Chem., Int. Ed*. **1971**, *19*, 435.
[9] Maghsoodlou, M. T.; Hazeri, N.; Habibi-Khorassani, S. M.; Solimani, V.; Marandi, G.; Razmjoo, Z. *J. Chem. Res*. **2008**, 198.
[10] Maghsoodlou, M. T.; Khandan-Barani, K.; Hazeri, N.; Habibi-Korassani, S. M.; C. Willis, A. *Res. Chem. Intermed*. **2012**, DOI 10.1007/s11164-012-1002-2.
[11] Khandan-Barani, K.; Maghsoodlou, M. T.; Habibi-Korassani, S. M.; Hazeri, N.; Sajadikhah, S. S. *Arkivoc*, **2011**, *xi*, 22.
[12] Khandan-Barani, K.; Maghsoodlou, M. T.; Sajadikhah, S. S. *Iran. J. Org. Chem*, **2013**, 5, 983.
[13] Hassanabadi, A.; Khandan-Barani, K.; *J. Chem. Res*. **2013**, *71*.
[14] Hazeri, N.; Maghsoodlou, M. T.; Habibi-Khorasani, S. M.; Ebrahimi, A.; Khandan-Barani, K.; Marandi, G.; Ziyadini, M.; Bijanzadeh, H. R.; Kazemian, M. A. *Iran. J. Org. Chem*, **2009**, 1, 33.
[15] Sheldon, R. G. *chem. Ind*. **1992**, 903.
[16] Winter feldt, E.; Schumann, D.; Dillinger, H. *J. Chem. Ber*. **1969**, *102*, 1656.
[17] Oakes, T. R.; David, H. G.; Nagel, F. *J. Am. Chem. Soc*. **1969**, *91*, 4761.
[18] Takisawa, T.; Obata, N.; Suzuki, Y.; Yanagida, T. *Tetrahedron Lett*. **1969**, 3407.
[19] Ugi, I. Isonitrile chemistry; Academic press, London, 1971.
[20] Ugi, I. *Angew. Chem*., Int. Ed. Engl. **1982**, *21*, 810.
[21] Yavari, I.; Maghsoodlou, M. T. *J. Chem. Res*. **1998**, 386.
[22] Nair, V.; Rajesh, C.; Vinod, A. U.; Bindu, S.; sreekanth, A. R.; mathen J. S.; Balagopal, L. *Acc. Chem. Res*. **2003**, *36*, 899.
[23] Shaabani, A.; Hossein-Rezayan, A.; Ghasemi, S.; Sarvary, A. *Tetrahedron Lett*. **2009**, *50*, 1456.
[24] Teimouri, M. B.; Mansouri, F.; Bazhrang, R. *Tetrahedron*. **2010**, *66*, 259.
[25] Marcaccini, S.; Torroba, T. *Org. Prep. Proc. Int*., **1993**, *25*, 141.