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Original Article

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An efficient one-pot synthesis of dimethyl 1-(Aryl)-5-cyano-4-(cyclohexylamino)-1,2,5,6-tetrahydro-6-oxopyridine-2,3-dicarboxylate derivatives

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Abstract:

The reactive 1:1 intermediate produced in the reaction between cyclohexyl isocyanide and electron- deficient acetylenic esters or dimethyl acetylene dicarboxylate was trapped by 2-cyano-N-(Aryl) acetamides to provides highly functionalized oxopyridine (potential synthetic and pharmaceutical interest) in acetonitrile under mild reaction conditions at ambient temperature after 24 h in fairly good yields. The structures of the products were corroborated spectroscopically (IR, 1H- and 13C-NMR), by EI - MS, and elemental analysis. A possible mechanism for this reaction is proposed. This present method carries the advantage that not only is the reaction performed under neutral conditions, but also the substances and reagents can be mixed without any modification or activation. The simplicity of this procedure and use of simple starting materialsmakes it an interesting alternative to other approaches.

Keywords: multicomponent reactions, cyanoacetamides, zwitterions, oxopyridine,

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1. Introduction:

Multi-component reactions (MCRs) have become a significant part of today's arsenal of methods in combinatorial chemistry due to their valued features, such as atom economy, straightforward reaction design, and the opportunity to construct target compounds by the introduction of several diversity elements in a single chemical event. Typically, purification of products resulting from MCRs is also simple since all the organic reagents employed are consumed and are incorporated into the target compound [1-3] .MCRs, leading to interesting heterocyclic scaffolds, are particularly useful for the construction of diverse chemical libraries of 'drug-like' molecules. The isocyanide-based MCRs are especially important in this area [4-5].

Recently, three-component reaction between isocyanides, electron-deficient acetylenic esters and organic compounds containing at least one acidic NH, OH or CH group have been reported [6-10]. These reactions usually passe through a zwiterionic intermediate to produce keteneimines which may be isolated as stable products or cyclize to heterocyclic compounds.

As part of our ongoing program to develop efficient and robust methods for the preparation of heterocyclic compounds, [11-14] herein we wish to report a fundamentally new approach to the synthesis of dimethyl 1-(Aryl)-5-cyano-4-(cyclohexylamino)-1,2,5,6-tetrahydro-6-oxopyridine-2,3-dicarboxylate by reaction between dimethyl acetylenedicarboxylate, cyclohexyl isocyanide, and of 2-cyano-*N*-(Aryl)acetamides in acetonitrile at ambient temperature after 24h in excellent yield.

2. Experimental:

Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a shimadzu IR-470 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker DRX-500 Avance spectrometer at solution in $CDCl_3$ using TMS as internal standard. The chemicals used in this work purchased from fluka (Buchs, Switzerland) and were used without further purification.

2.1 General Procedure

To a magnetically stirred solution of cyclohexyl isocyanide (1 mmol) and 2-cyano-*N*-(Aryl)acetamides (1 mmol) in acetonitrile (10 ml) was added a solution of dimethyl acetylenedicarboxylate (1 mmol) in acetonitrile (5 ml) dropwise at r.t. over 10 min. The mixture was then allowed to stir for 24 h. The solvent was removed under reduced pressure, and the residue was separated by column chromatography (silica gel, hexane–EtOAc, 5:1) to afford the pure title compounds.

2.2 Spectral data

Dimethyl 1-(5-bromopyridin-2-yl)-5-cyano-4-(cyclohexylamino)-1,2,5,6-tetrahydro-6-oxopyridine-2,3-dicarboxylate **(4a):**

Yellow oil; Yield 0.39 g (80%); IR (KBr) (ν_{max}, cm^{-1}): 2205 (CN), 1723, 1684 (C=O, ester). Analyses: Calcd. for $C_{21}H_{23}BrN_4O_5$: C, 51.33; H, 4.72; N, 11.40%. Found: C, 51.43; H, 4.85; N, 11.37%. MS (m/z, %): 490(M^+, 9). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.10-1.95 (10 H, m, 5 CH_2 of cyclohexyl), 3.38 (1 H, m, CH of cyclohexyl), 3.63 (3 H, s, OCH_3), 3.64 (3 H, s, OCH_3), 4.37 (1 H, s, CH), 6.03 (1 H, d, $^3J_{HH}$ = 8.5 Hz, NH), 6.27 (1 H, s, CH), 7.67(1 H, dd, $^3J_{HH}$ = 8.9 Hz, $^4J_{HH}$ = 2.3 Hz, 1 CH of 4-Br C_5H_3N), 8.04 (1 H, d, $^3J_{HH}$ = 8.9Hz, 1 CH of 4-Br C_5H_3N), 8.26(1 H, s, 1 CH of 4-Br C_5H_3N) ppm. ^{13}C NMR (125.7MHz, $CDCl_3$): 25.06, 25.21, 25.30, 33.28, 34.65 (5 CH_2 of cyclohexyl), 43.93 (CH of cyclohexyl), 54.00(CH), 54.23 (OCH_3), 54.58 (OCH_3), 56.83 (CH), 115.45, 116.02, 117.25, 119.23, 140.33, 148.14, 151.11,160.33 (C arom, aliphatic, CN), 162.05, 166.61,170.25 (3CO) ppm.

Dimethyl 1-(5-cholropyridin-2-yl)-5-cyano-4-(cyclohexylamino)-1,2,5,6-tetrahydro-6-oxopyridine-2,3-dicarboxylate **(4b):**

Yellow oil; Yield 0.34 g (78%); IR (KBr) (ν_{max}, cm^{-1}): 2208 (CN), 1733, 1685 (C=O, ester). Analyses: Calcd. for $C_{21}H_{23}ClN_4O_5$: C, 56.44; H, 5.19; N, 12.54%. Found: C, 56.14; H, 5.32; N, 12.26%. MS (m/z, %): 446 (M^+, 11). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.10-1.87 (10 H, m, 5 CH_2 of cyclohexyl), 3.36 (1 H, m, CH of cyclohexyl), 3.62 (3 H, s, OCH_3), 3.66 (3 H, s, OCH_3), 4.32 (1 H, s, CH), 6.11 (1 H, d, $^3J_{HH}$ = 8.5

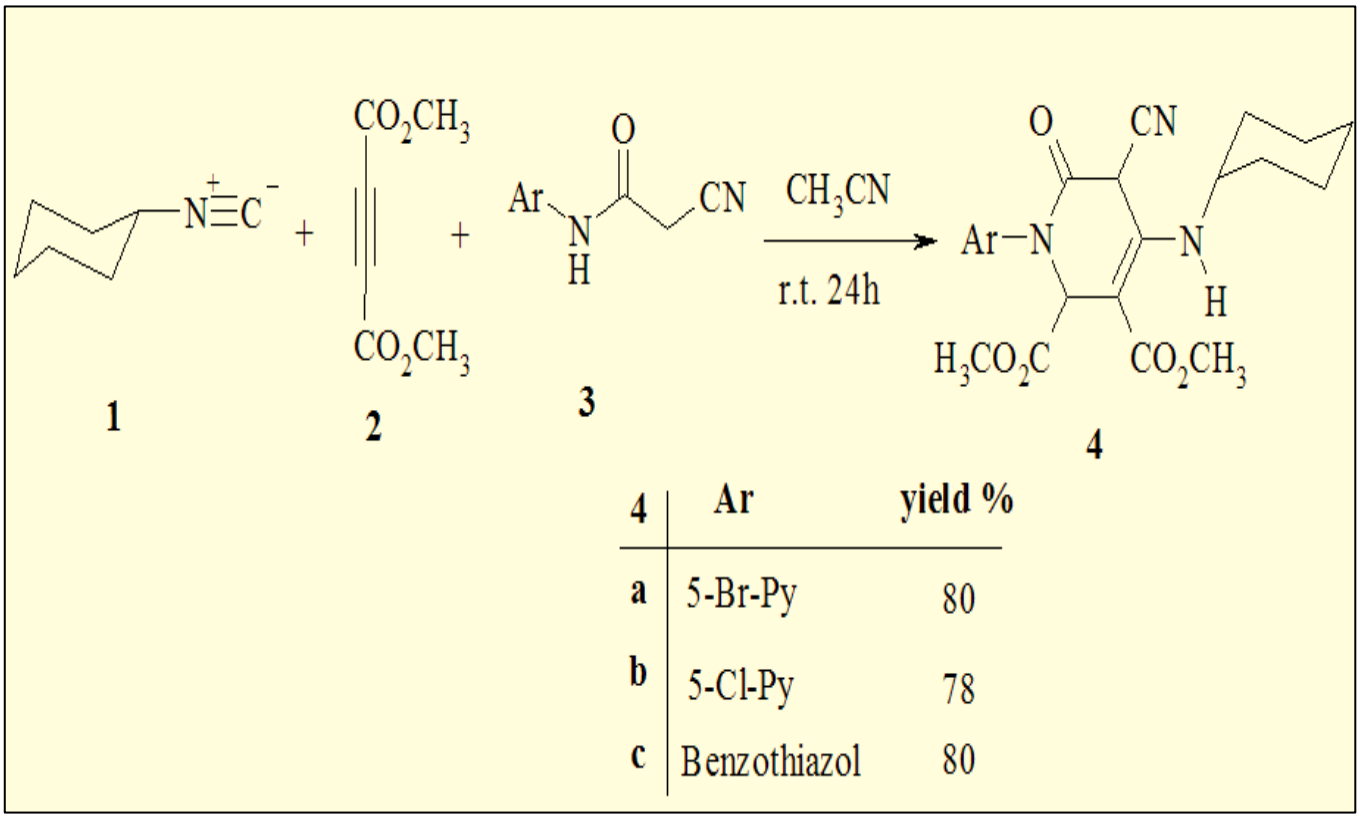
Hz, NH), 6.26 (1 H, s, CH), 7.65(1 H, dd, $^3J_{HH}$ = 8.9 Hz, $^4J_{HH}$ = 2.3 Hz, 1 CH of 4-Cl C_5H_3N), 8.07 (1 H, d, $^3J_{HH}$ = 8.9Hz, 1 CH of 4-Cl C_5H_3N), 8.25 (1 H, d, 1 CH of 4-Cl C_5H_3N) ppm. ^{13}C NMR (125.7MHz, $CDCl_3$): 25.14, 25.23, 25.33, 33.28, 34.66 (5 CH_2 of cyclohexyl), 43.90 (CH of cyclohexyl), 54.16(CH), 54.23 (OCH_3), 54.59 (OCH_3), 56.78 (CH), 114.23, 116.14, 117.25, 119.22, 140.31, 148.22, 151.12, 161.01 (C arom, aliphatic, CN), 162.18 , 166.62, 170.21 (3CO) ppm.

*Dimethyl 1-(benzo[d]thiazol-2-yl)-5-cyano-4-(cyclohexylamino)-1,2,5,6-tetrahydro-6-oxopyridine-2,3-dicarboxylate***(4c):**

Yellow oil; Yield 0.37 g (80%); IR (KBr) (ν_{max}, cm^{-1}): 2205 (CN), 1733, 1662 (C=O, ester). Analyses: Calcd. for $C_{23}H_{24}N_4O_5S$: C, 58.96; H, 5.16; N, 11.96% Found: C, 58.82; H, 5.31; N, 11.79%. MS (m/z, %): 468 (M^+, 7). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.06-1.91 (10 H, m, 5 CH_2 of cyclohexyl), 3.39 (1 H, m, CH of cyclohexyl), 3.57 (3 H, s, OCH_3), 3.58 (3 H, s, OCH_3), 4.37 (1 H, s, CH), 4.18 (1 H, d, $^3J_{HH}$ = 8.2 Hz, NH), 6.42 (1 H, s, CH), 7.12-8.03 (4H, m, arom) ppm. ^{13}C NMR (125.7MHz, $CDCl_3$): 24.17, 24.45, 25.50, 31.27, 33.10 (5 CH_2 of cyclohexyl), 43.36 (CH of cyclohexyl), 48.02 (CH), 53.22 (OCH_3), 53.91 (OCH_3), 57.32 (CH), 117.27, 121.80, 123.99, 124.38, 126.07, 126.55, 133.94, 148.28, 157.14,159.15 (C arom, aliphatic, CN), 162.56 , 167.61, 169.17 (3CO) ppm.

3. RESULTS AND DISCUSSION

The reaction of cyclohexyl isocyanide **1** with dimethyl acetylenedicarboxylate **2** in the presence 2-cyano-*N*-(Aryl)acetamides **3** proceed with a smooth 1:1:1 addition reaction in acetonitrile at ambient temperature, to produce dimethyl 1-(Aryl)-5-cyano-4-(cyclohexylamino)-1,2,5,6-tetrahydro-6-oxopyridine-2,3-dicarboxylate **4** in 78–80% yields (Scheme 1).



4	Ar	yield %
a	5-Br-Py	80
b	5-Cl-Py	78
c	Benzothiazol	80

Scheme 1

The structures of compounds **4a-c** were deduced from their mass spectra, elemental analyses, IR, and high-field ^{1}H and ^{13}C NMR spectra.

The mass spectrum of compound **4a** displayed the molecular-ion peak at *m*/*z* = 490.

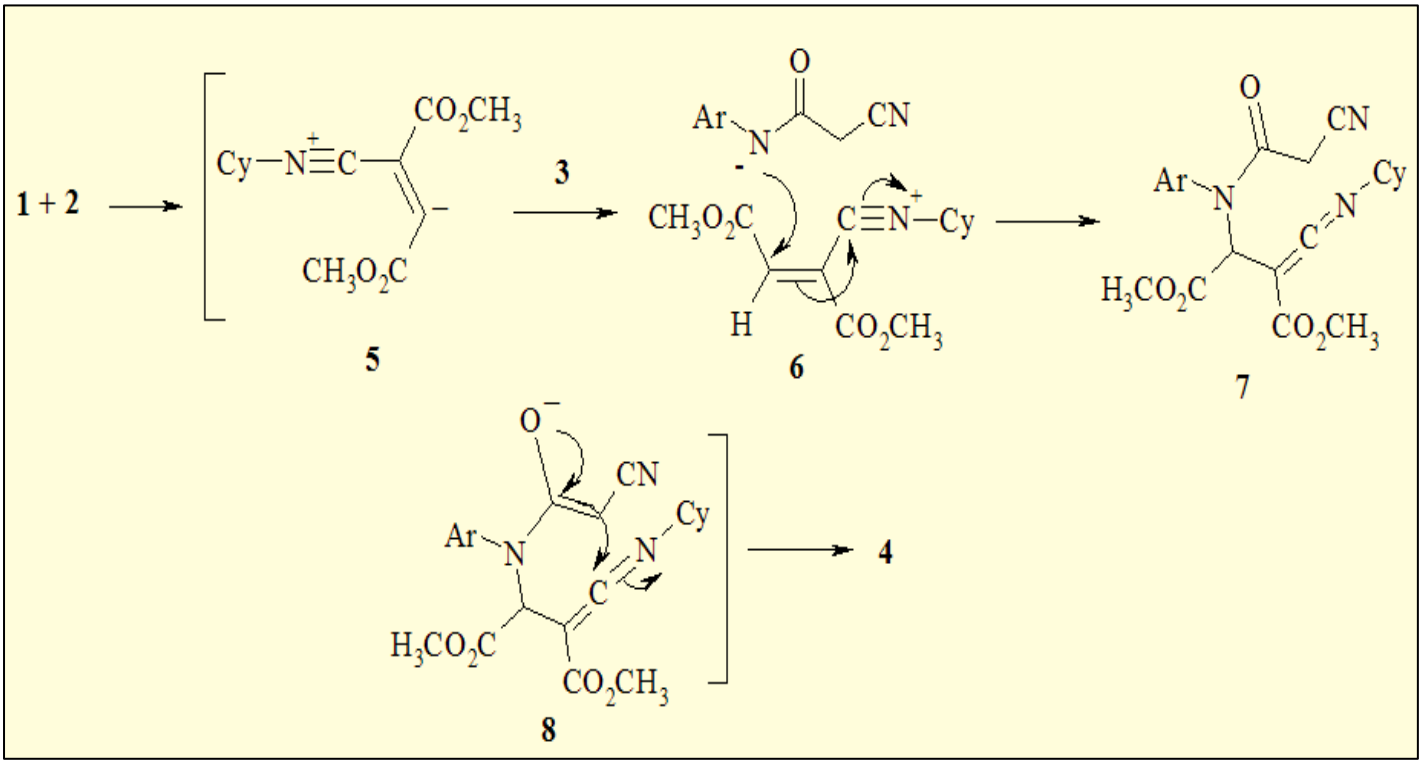
The ^{1}H NMR spectrum of compound **4a** consisted of multiplet signals for the cyclohexyl rings at δ =1.10-1.95 ppm (10H, m, $5CH_2$) and a multiplet for N-CH of cyclohexyl ringat δ = 3.38 ppm. Four single signals were observed for two methoxy groups at δ = 3.63, 3.64 ppm and two methine at δ = 4.37, 6.27 ppm. A doublet signal at δ = 6.03 ppm ($^{3}J_{HH}$ = 8.2 Hz) was observed for the NH proton. The aromatic protons were observed at δ = 7.67 ppm (1 H, dd, $^{3}J_{HH}$ = 8.9Hz, $^{4}J_{HH}$ = 2.3 Hz), and δ = 8.04 ppm (1 H, d, $^{3}J_{HH}$ = 8.9Hz) and 8.26 ppm (1 H, s).

The structural assignments made on the basis of the NMR spectra of compound **4a** were supported by its IR spectrum, the ester carbonyl groups exhibited strong absorption bands at 1723 and 1684 $cm^{-1}$and cyanid group at 2235 cm^{-1}.

The ^{13}CNMR spectrum of compound **4a** showed 21 distinct resonances in agreement with the proposed structure. Partial assignments of these resonances are given in the experimental section.

Although we have not established the mechanism of the reaction between cyclohexyl isocyanide and dimethyl acetylenedicarboxylate in the presence of the 2-cyano-*N*-(Aryl)acetamides in an experimental manner, a possible explanation is proposed in (Scheme 2).

On the basis of the well established chemistry of isocyanides [4-5,15-18] it is reasonable to assume that compounds **4** result from nucleophilic addition of isocyanide to the acetylenic system and subsequent protonation of the 1:1 adduct **5** by the NH-acid. Then, the positively charged ion **6** is attacked by the anion of the NH-acid to form ketenimine **7**. Such an addition product may tautomerize and then cyclize, under the reaction conditions employed, to produce **4**.



Scheme 2

4. Conclusion

In conclusion, we have developed an efficient synthetic method for the preparation of highly functionalized oxopyridine. The present reaction is performed under neutral conditions and starting materials and reagent can be reacted without any prior activation.

5. Acknowledgements

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