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Green synthesis of amide derivatives by using activated acetylenic compounds and amines

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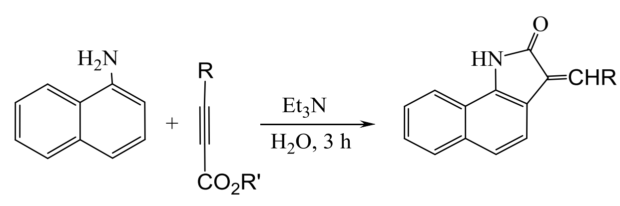
Abstract: The reaction between activated acetylenic compounds and various amines in the presence of Et_3N leads to lactam derivatives in good yields. The present protocol offers the advantages of clean reaction, short reaction time, high yield, easy purification and performing without the catalyst.

Keywords: Lactams, Aniline, Naphthol amin, Dialkyl acetylenedicarboxylates.

Introduction

The heterocyclic compounds containing spiro moiety because of their rigidity and considerable biological characteristics are particularly significant [1]. Making spiro heterocyclic compounds is significant and intriguing because this structure is also shown in natural alkaloids [2]. The heterocyclic compounds in among organic compounds have well-known position for showing many biological properties [3-15]. One strategy for the preparation of heterocyclic compounds is multicomponent reaction (MCRs), which could produce these compounds with significant biological activity in one pot and high yields compared with reactions with more stages [16, 17]. MCRs have many advantages over different process reactions, such as good product performance, easy removal and atom economy, and short reaction time [18-20]. The utilizing of principles for decrease or delete the employing of dangerous starting materials for performing reactions named green chemistry [21].

The many subjects such as synthesis, solvents, catalysis, raw materials, products and efficient processes are covered by green chemistry. In our quest for developing new techniques to synthesize new heterocyclic compounds [22-30], herein, we considered a green process for the generation of some cyclic amides **3** via a good and one-pot reaction of naphthol amines **1** and activated acetylenic compounds **2** in the presence of Et_3N at room temperature in high yields (Scheme 1).



Scheme 1. Synthesis of lactams

Results and discussion

We now report a synthesis of lactam derivatives **3** through the reaction of activated acetylenic compounds

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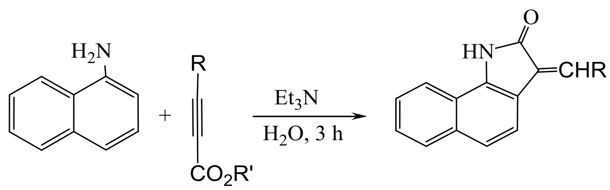
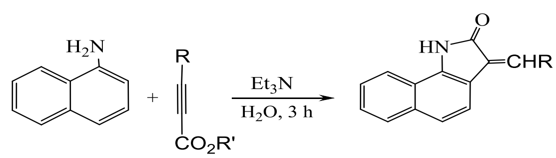
with cyclic amines in the presence of Et_3N in high yields (Scheme 1). Our results are summarized in Table 1. The reaction of aniline **1a** with electron deficient acetylenic compounds in the presence of Et_3N at room temperature leads to the lactam derivative **3** in 85% yield (Table **1**). No other compound was obtained from the residue by column chromatography. The structure of the product was deduced from its elemental analyses and its IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data. The ^{1}H NMR spectrum of **3a** exhibited two singlets identified as methoxy (δ = 3.75 ppm) and olefinic (δ = 7.02 ppm) protons along with multiplets (δ = 6.65, 7.23, 7.31, and 7.48 ppm) for the aromatic protons. The ^{13}C NMR spectrum of **3a** showed eleven distinct resonances in agreement with the proposed structure. Also, The ^{1}H NMR spectrum of **3d** exhibited two singlets identified as methoxy (δ = 3.88 ppm) and olefinic (δ = 6.67 ppm) protons along with multiplets (δ = 7.27-8.46 ppm) for the aromatic protons. The OH proton resonance appears at δ = 9.34 ppm. The ^{13}C NMR spectrum of **3d** showed 15 distinct resonances in agreement with the proposed structure.

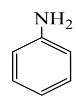
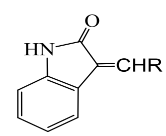
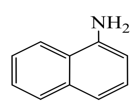
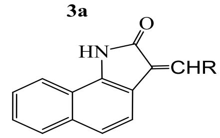
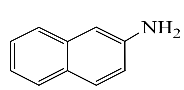
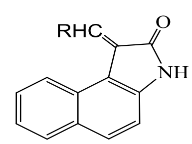
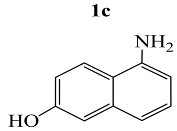
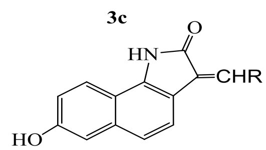
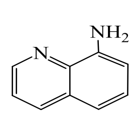
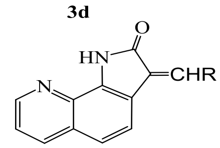


1 **2** **3**

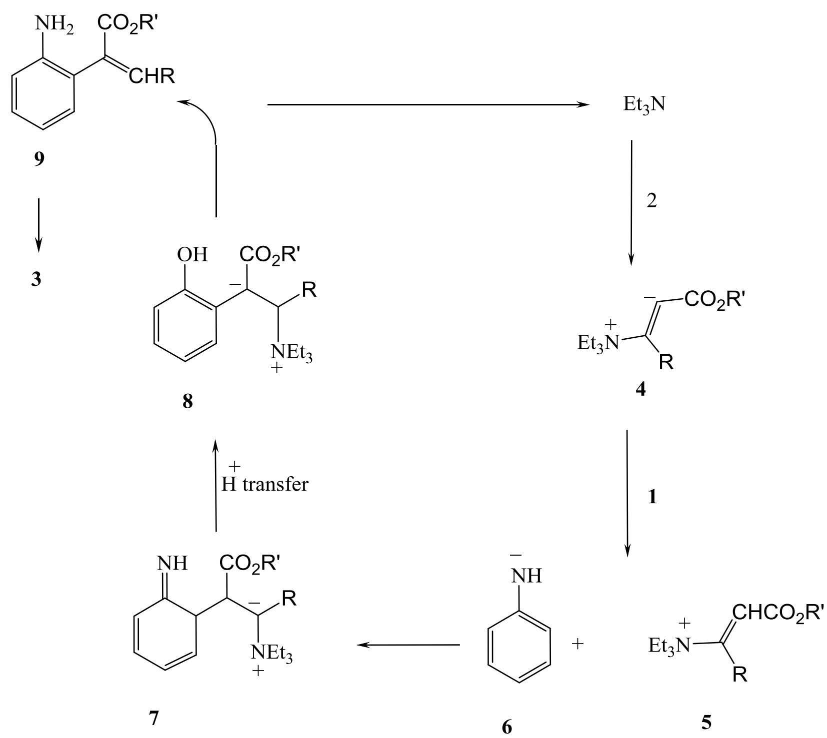
Table 1: Reaction of activated acetylenic compounds with cyclic amines



1 **2** **3**

Entry	Starting materials	Product	Yield (%)
1	 **1a**	 **3a**	85
2	 **1b**	 **3b**	85
3	 **1c**	 **3c**	80
4	 **1d**	 **3d**	80
5	 **1e**	 **3e**	82

A possible mechanism for the formation of 3a is proposed in Scheme 1. It is reasonable to assume that 3a results from initial addition of Et3N to the acetylenic ester and subsequent protonation of the 1,3-dipolar intermediate 4 by 1a. Then, the positively charged ion 5 might be attacked by the conjugated base of the NH-acid to produce the nitrogen ylide 7, which undergoes proton-transfer reaction to produce 8. The 1,3-dipolar ion 8 is converted to 9 by elimination of Et3N. The product 3a is formed by intramolecular lactonization of 9. Similar mechanism can be proposed for the formation of 3b-3e.



Scheme1: Proposed mechanism for formation of **3**

Conclusion

In summary, the reaction between activated acetylenic compounds and cyclic amines leads to lactam derivatives in excellent yields. The presented one-pot reaction carries the advantage that not only is the reaction performed under neutral conditions, but the substances can be mixed without any activation or modification.

Experimental section

Typical procedure for the synthesis of **3a**: To a stirred solution of **1a** (0.21 g, 2 mmol) and activated acetylenic compounds **2** (2 mmol) in 10 mL water was added Et_3N (5 mL) at room temperature. The reaction mixture was then stirred for 3 h. The solvent was removed under reduced pressure and the residue was separated by silica gel column chromatography (Merck 230-400 mesh) using *n*-hexane-EtOAc (4:1) as eluent to give **3**.

Compound **3a**: Yellow oil; yield 0.38 g, 93%. IR (KBr) (ν_{max}/cm^{-1}): 1735 and 1650 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$): δ= 3.72 (3 H, s, OMe), 6.65 (1 H, d, $^3J_{HH}$ =7.9 Hz, CH), 7.01 (1 H, s, CH), 7.23 (1 H, dd, $^3J_{HH}$ = 7.9 Hz, $^3J_{HH}$ = 7.5 Hz, CH), 7.31(1 H, dd, $^3J_{HH}$ = 7.8 Hz, $^3J_{HH}$ = 7.5 Hz, CH), 7.48 (1 H, d, $^3J_{HH}$ =7.8 Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 52.6 (OCH_3), 111.2 (CH), 122.1 (CH), 123.1 (CH), 123.5 (C), 124.3 (CH), 130.6 (CH), 138.2 (C), 153.5 (C), 165.3 (C=O), 166.5 (C=O) ppm. MS (EI, 70 eV): *m*/*z* (%) = 204 (M^+, 12), 189 (17), 160 (47), 145 (73), 144 (36), 132 (100), 91 (14), 76 (68), 59 (42). Anal. Calcd for $C_{11}H_8O_4$ (204.2): C, 64.71; H, 3.95%. Found: C, 65.18; H, 3.99%.

Compound **3b**: Brown crystals, mp 176-178 °C, yield 0.48 g, 94%. IR (KBr) (ν_{max}/cm^{-1}): 1715 and 1616

(C=O). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.02 (3 H, s, OMe), 6.94 (1 H, s, CH), 7.59 (1 H, dd, $^3J_{HH}$ = 7.6 Hz, $^3J_{HH}$ = 6.9 Hz, CH), 7.62 (1 H, dd, $^3J_{HH}$ = 7.6 Hz, $^3J_{HH}$ = 5.1 Hz CH), 7.63 (1 H, d, $^3J_{HH}$ = 5.1 Hz, CH), 7.81 (1 H, d, $^3J_{HH}$ = 6.3 Hz, CH), 8.10 (1 H, d, $^3J_{HH}$ = 6.9 Hz, CH), 8.46 (1 H, d, $^3J_{HH}$ = 6.3 Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 53.2 (OCH_3), 111.4 (CH), 118.2 (C), 121.7 (CH), 122.5 (CH), 122.9 (C), 124.5 (CH), 127.2 (CH), 127.6 (CH), 129.2 (CH), 134.8 (C), 143.2 (C), 151.7 (C-O), 159.9 (C=O), 164.5 (C=O) ppm. MS (EI, 70 eV): *m*/*z* (%) = 254 (M^+, 5), 251 (22), 223 (100), 195 (38), 135 (56), 113 (84), 109 (54), 55 (78). Anal. Calcd for $C_{15}H_{10}O_4$ (254.2): C, 70.86; H, 3.96%. Found: C, 70.40; H, 3.81%.

Compound **3c**: Green powder, mp 113-115 °C, yield 0.46 g, 90%. IR (KBr) (ν_{max}/cm^{-1}): 1724 and 1620 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.06 (3 H, s, OMe), 6.59 (1 H, s, CH), 7.46 (1 H, d, $^3J_{HH}$ = 8.1 Hz, CH), 7.55 (1H, dd, $^3J_{HH}$ = 7.2 Hz, $^3J_{HH}$ = 6.1 Hz, CH), 7.64 (1 H, dd, $^3J_{HH}$ = 7.2 Hz, $^3J_{HH}$ = 8.1 Hz, CH), 7.77 (1 H, d, $^3J_{HH}$ = 8.4 Hz, CH), 7.92 (1 H, d, $^3J_{HH}$ = 6.1 Hz, CH), 8.02 (1 H, d, $^3J_{HH}$ = 8.4 Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 53.5 (OCH_3), 110.1 (CH), 115.5 (CH), 117.3 (CH), 123.3 (C), 126.1 (CH), 127.9 (CH), 128.1 (CH), 129.4 (C), 130.9 (C), 134.6 (CH), 145.9 (C), 154.9 (C), 159.5 (C=O), 167.8 (C=O) ppm. MS (EI, 70 eV): *m*/*z* (%) = 254 (M^+, 10), 251 (45), 223 (100), 135 (50), 113 (84), 109 (65), 55 (75). Anal. Calcd for $C_{15}H_{10}O_4$ (254.2): C, 70.86; H, 3.96%. Found: C, 70.39; H, 3.82%.

Compound **3d**: Orange powder, mp 187-189 °C, yield 0.46 g, 85%. IR (KBr) (ν_{max}/cm^{-1}): 3435 (OH), 1712 and 1617 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.89 (3 H, s, OMe), 6.67 (1 H, s, CH), 7.27 (1 H, d, $^4J_{HH}$ = 3.2 Hz, CH), 7.29 (1 H, dd, $^3J_{HH}$ = 8.7 Hz, $^4J_{HH}$ = 3.2 Hz, CH), 7.50 (1 H, d, $^3J_{HH}$ = 8.5 Hz, CH), 7.96 (1 H, d, $^3J_{HH}$ = 8.7 Hz, CH), 8.45 (1 H, d, $^3J_{HH}$ = 8.5 Hz, CH), 9.34 (1 H, s, OH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 52.6 (OCH_3), 111.3 (CH), 114.2 (C), 114.4 (CH), 120.5 (CH), 121.9 (C), 123.0 (CH), 124.7 (CH), 124.9 (CH), 124.9 (C), 134.9 (C), 139.7 (C), 151.7 (C), 159.9 (C=O), 164.4 (C=O). MS (EI, 70 eV): *m*/*z* (%) = 270 (M^+, 20), 242 (100), 239 (26), 211 (78), 155 (100), 126 (42), 77 (26). Anal. Calcd for $C_{15}H_{10}O_5$ (270.2): C, 66.67; H, 3.73%. Found: C, 66.91; H, 3.65%.

Compound **3e**: Pale yellow crystals, mp 155-157 °C, yield 0.44 g, 86%. IR (KBr) (ν_{max}/cm^{-1}): 1714 and 1619 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.91 (3 H, s, OMe), 7.2 (1 H, s, CH), 7.35 (1 H, d, $^3J_{HH}$ = 8.5 Hz, CH), 7.45 (1 H, dd, $^3J_{HH}$ =8.5 Hz, $^3J_{HH}$ = 6.7 Hz, CH), 7.50 (1 H, d, $^3J_{HH}$ = 7.2 Hz, CH), 8.15 (1 H, d, $^3J_{HH}$ = 6.7 Hz, CH), 8.78 (1 H, d, $^3J_{HH}$ = 7.2 Hz, CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 52.8 (OCH_3), 112.7 (CH), 116.9 (C), 117.6 (CH), 122.1 (CH), 127.9 (C), 129.4 (C), 136.1 (CH), 137.95 (C), 148.2 (CH), 148.2 (CH), 150.4 (C), 159.5 (C=O), 164.4 (C=O) ppm. MS (EI, 70 eV): *m*/*z* (%) = 255 (M^+, 5), 224 (100), 195 (45), 128 (65), 109 (54), 77 (24), 59 (78), 31 (52). Anal. Calcd for $C_{14}H_9NO_4$ (255.2): C, 65.88; H, 3.55%. Found: C, 65.50; H, 3.46%.

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