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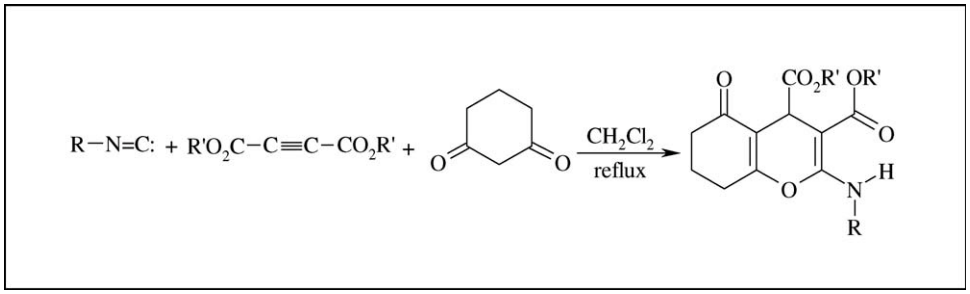
Received October 12, 2009
DOI 10.1002/jhet.401
Published online 8 June 2010 in Wiley InterScience (www.interscience.wiley.com).



Cyclohexyl isocyanides react with dialkyl acetylenedicarboxylates in the presence of CH-acids such as cyclohexane-1,3-dione or *N*,*N*′-dimethylbarbituric acid in one-pot to afford 4*H*-pyran annulated heterocyclic systems in fairly high yields.

J. Heterocyclic Chem., **47**, 857 (2010).

INTRODUCTION

In the meantime multicomponent reactions are well established as a powerful tool for the rapid construction of complex and structurally diverse compounds from relatively simple building blocks [1]. High atom-economy, chemical efficiency, and convergence are typical features of such one-pot condensations of at least three different starting materials. Because of the remarkable high purity of libraries, multicomponent reactions are well-suited for both combinatorial chemistry [2] and high-speed parallel synthesis and therefore possess high exploratory power [3]. Amongst the known multicomponent reactions, isocyanide based MCRs such as the versatile Ugi and Passerini reactions are especially valuable [4]. Especially isocyanide-based [5] and asymmetric [6] multicomponent reactions have been emerging fields of interest in the last decade, but the construction of heterocycles via multicomponent reactions was also in the focus recently [7]. However, there are only a few applications of multicomponent reactions in dihydroindeno[1,2-b]pyran so far [8]. In our Laboratory, isocyanide-based multicomponent reactions of CH-acids have just recently been key instruments for the rapid synthesis of the novel pyran ring systems of pyrimidine, indeno, and 4*H*-chromene. Herein we report how such reactions contributed significantly to the synthesis of the novel heterocyclic compounds.

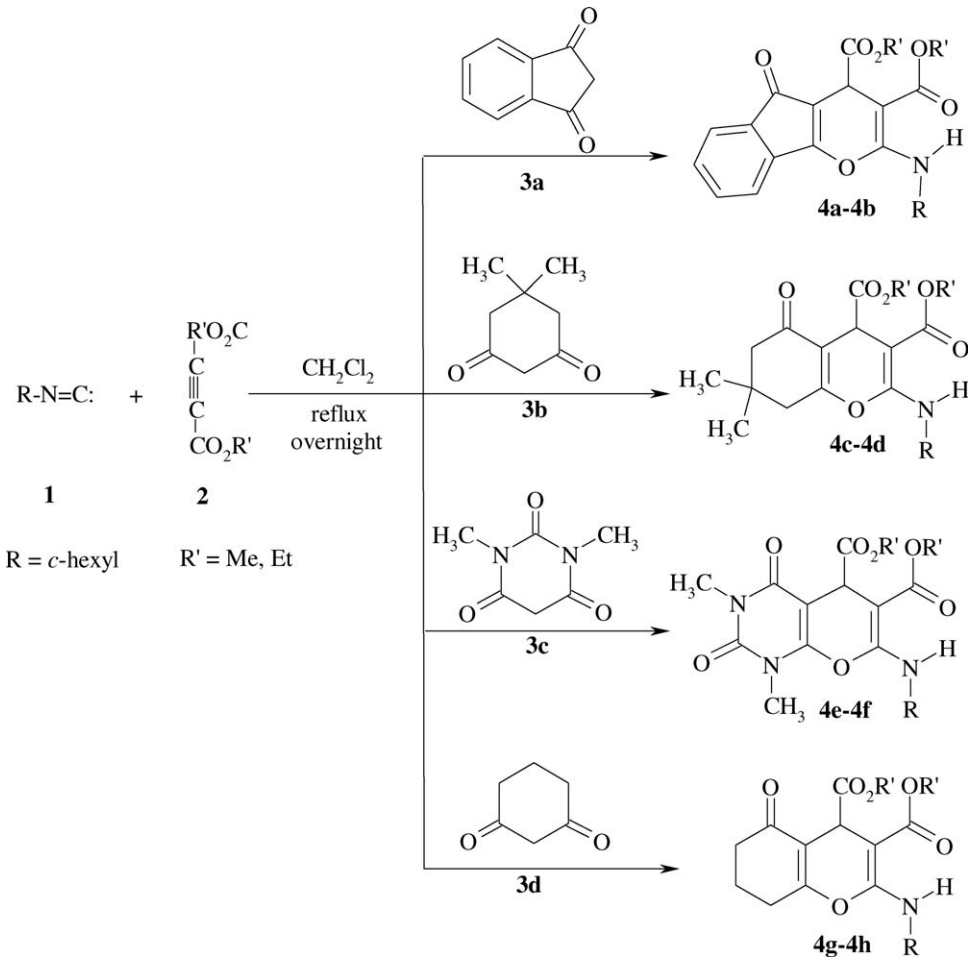
RESULTS AND DISCUSSION

The one-pot three component condensation reactions of alkyl isocyanides **1** with electron-deficient acetylenic esters **2** in the presence of CH-acids **3a–d** proceeded in anhydrous dichloromethane and was completed after 12 h to afford corresponding heterocyclic systems **4a–h**, in moderate to good yields (65–90%). ^{1}H NMR and ^{13}C NMR spectra of the crude products clearly indicated the formation of heterocyclic compounds **4a–h**. The structures of the products **4a–h** were deduced from their elemental analyses, IR, ^{1}H NMR, and ^{13}C NMR spectra. The mass spectra of compounds **4a–h** displayed molecular ion peak at appropriate *m*/*z* values. Initial fragmentations involved loss from or complete loss of the side chains and scission of heterocyclic system.

The ^{1}H NMR spectrum of **4a** consisted of a multiplet of signals for the cyclohexyl ring (δ = 1.13–1.90 ppm) and two single sharp lines for methoxy groups (δ = 3.70 and 3.73 ppm). A multiplet resonance is observed for the N—CH group (δ = 3.82 ppm), and a single sharp line for methine proton (δ = 4.38 ppm). A fairly broad singlet (δ = 8.90 ppm) was observed for the NH group. The presence of an amine proton was confirmed by exchange with D_2O. The chemical shift of the N—H group indicates that this moiety must have participated in a six-member intramolecular hydrogen bond formation with the vicinal carbonyl group as shown in Scheme 1.

The ^{1}H decoupled ^{13}C NMR spectrum of **4a** showed 20 sharp signals in agreement with proposed structure. Compound **4a** possesses a highly polarized carbon-carbon double bond. The β-carbon of this enaminone system appears about 72–77 ppm. These signals along with the downfield shift of the NH proton, support the enaminone structure **4**. The ^{1}H NMR and ^{13}C NMR spectra of

Scheme 1

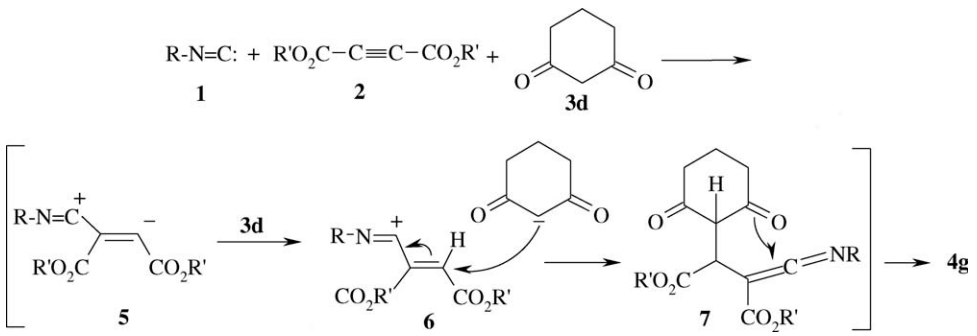


4b–h are similar to those of **4a**, except for the CH-acids and ester moieties. Partial assignments of these resonances are given in the experimental section.

The structural assignments made on the basis of the ^{1}H NMR and ^{13}C NMR spectra of **4a** was supported by measurement of its IR spectra. The IR spectrum of **4a** showed strong absorption at 3420, 1737, and 1678 cm^{-1} due to the N—H and carbonyls groups.

A plausible mechanism for formation of **4g** is shown in Scheme 2. On the basis of the well established chemistry of isocynides [4] it is reasonable to assume that compound **4g** results from initial addition of alkyl isocyanide **1** to the acetylenic ester to form intermediate **5**. Protonation of **5** by **3d** and subsequent attack of the resulting nucleophile generated to the positively charged ion **6** afforded ketenimine **7** (Scheme 2). Such an

Scheme 2



addition product may tautomerize and cyclize, under the reaction conditions employed, to produce **4g**.

In conclusion, the three-component reaction of alkyl isocyanides with electron-deficient acetylenic esters in the presence of CH-acids provides a simple entry into the synthesis of 4*H*-pyran annulated heterocyclic systems of potential synthetic interest. The present procedure carries the advantage that, not only is the reaction performed under neutral conditions, but also the substances can be mixed without any activation or modification.

EXPERIMENTAL

Dialkyl acetylenedicarboxylates, alkyl isocyanides, and other reagents and solvents used in this work were obtained from Fluka (Buchs, Switzerland) and used without further purification. NMR spectra were recorded with a Bruker DRX-300 AVANCE instrument (299.9 MHz for ^{1}H and 75.4 MHz. for ^{13}C) with $CDCl_3$ as solvent. Chemical shifts are given in ppm (δ) relative to internal TMS, and coupling constant (*J*) are reported in hertz (Hz). Melting points were measured with an electrotherma1 9100 apparatus. Elemental analyses for C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer. These results agreed favorably with the calculated values. Mass spectra were recorded with a Shimadzu QP-GC Mass 5050 spectrometer operating at an ionization potential of 70 eV. IR spectra were measured with Bruker Tensor 27 spectrometer.

Typical procedure for preparation of compounds 4a–h. To a stirred solution of 0.145 g indan-1,3-dione (1 mmol) and 0.142 g dimethyl acetylendicarboxylate (1 mmol) in 10 mL dichloromethane, was added, 0.109 g *c*-hexyl isocyanide (1 mmol) in 2 mL dichloromethane at room temperature over 4 min via a syringe. The reaction mixture was heated at reflux for 12 h. The solvent was removed and the residue was purified by silica gel (Merck silica gel 60, 70–230 mesh) column chromatography using hexane/ethyl acetate (8:2) as eluent.

Data. ***Dimethyl 2-(cyclohexylamino)-5-oxo-4,5-dihydroindeno [1,2-b]pyran-3,4-dicarboxylate (4a)*** Dark brown powder (0.258 g, 65%), mp 212–214°C. IR (KBr) (ν_{max}/cm^{-1}): 3420 (NH), 1737, 1678, and 1670 (C=O), 1235 and 1215 (C—O). ^{1}H NMR: δ = 1.13–1.90 (10 H, m, 5 CH_2), 3.70 (3 H, s, OCH_3), 3.71 (3 H, s, OCH_3), 3.73 (1 H, m, N—CH), 4.38 (1 H, s, CH), 7.17 (1 H, m, CH), 7.34 (1 H, m, CH), 7.40 (1 H, m, CH), 7.48 (1 H, m, CH), 8.90 (1 H, br d, $^3J_{HH}$ = 5.6 Hz, NH). ^{13}C NMR: δ = 24.5, 25.5, 33.9 (5 CH2), 43.5 (CH), 50.5 (CHN), 51.2 and 52.5 (2 OCH3), 72.6 (N—*C*=C), 107.8 (O—C=*C*), 118.1 (CH), 122.4 (CH), 130.7 (CH), 131.8 (C), 132.6 (CH), 135.9 (C) 159.4 and 167.2 (2 O—*C*=C), 169.9, 173.3 and 190.7 (3 C=O). MS (EI, 70 eV): *m*/*z* (%) = 397 (M$^+$, 8), 384 (65), 348 (100), 289 (35), 108 (23), 59 (31). Anal. Calcd. for $C_{22}H_{23}NO_6$ (397.4): C, 66.49; H, 5.83; N, 3.52%; Found: C, 66.98; H, 5.78; N, 3.59.

Diethyl 2-(cyclohexylamino)-5-oxo-4,5-dihydroindeno[1,2-b]pyran-3,4-dicarboxylate (4b). Black oil (0.297 g, 70%). IR (KBr) (ν_{max} /cm^{-1}): 3418 (NH), 1728, 1683, and 1660 (C=O), 1607 (C=O), 1241 (C—O). ^{1}H NMR: δ = 1.26 and 1.27 (6 H, 2 t, $^3J_{HH}$ = 7.5 Hz, 2 CH_3), 1.38–2.10 (10 H, m, 5 CH_2), 3.80 (1 H, m, N—CH), 4.15 and 4.19 (4 H, 2 q, $^3J_{HH}$ = 7.5 Hz, 2 OCH_2), 4.39 (1 H, s, CH), 7.18 (1 H, m, CH), 7.35 (1 H, m, CH), 7.40 (1 H, m, CH), 7.46 (1 H, m, CH), 8.19 (1 H, br d, $^3J_{HH}$ = 5.5 Hz, NH). ^{13}C NMR: δ = 14.2 and 14.5 (2 CH_3), 24.5, 25.5, 33.9 (5 CH_2), 43.5 (CH), 50.5 (CHN), 59.6 and 60.9 (2 OCH_2), 72.5 (N—*C*=C), 107.6 (O—C=*C*), 118.1 (CH), 122.4 (CH), 130.7 (CH), 131.8 (C), 132.6 (CH), 135.9 (C), 159.4 and 167.3 (2 O—*C*=C), 169.9, 173.3 and 190.7 (3 C=O). MS (EI, 70 eV): *m*/*z* (%) = 425 (M$^+$, 5), 409 (12), 352 (100), 342(94), 83 (55), 73 (47). Anal. Calcd. for $C_{24}H_{27}NO_6$ (425.47): C, 67.75; H, 6.40; N, 3.29%; Found: C, 67.8; H, 6.5; N, 3.3.

Dimethyl 2-(cyclohexylamino)-5-oxo-7,7-dimethyl 5,6,7,8-tetrahydro-4H-chromene-3,4-dicarboxylate (4c). Yellow powder (0.294 g, 0.75%), mp 140–142°C. IR (KBr) (ν_{max} /cm^{-1}): 3423, (N—H) 1761, and 1726 (C=O), 1605 (C=C). ^{1}H NMR ($CDCl_3$): δ = 1.10 and 1.12 (6 H, 2 s, 2 CH_3), 1.18–1.90 (10 H, m, 5 CH_2), 2.25 and 2.42 (4 H, 2 s, 2 CH_2), 3.58 and 3.61 (6 H, 2 s, 2 OCH_3), 3.70 (1 H, m, NCH), 4.49 (1 H, s, CH), 8.58 (1 H, d, $^3J_{HH}$ = 7.2 Hz, NH). ^{13}C NMR ($CDCl_3$): δ = 24.4, 25.5 and 33.6 (5 CH_2), 27.1 and 29.3 (2 CH_3), 32.3 (*C*M_2), 34.4 (CH), 40.7 and 50.8 (2 CH_2), 49.9 (N—CH), 50.5 and 52.2 (2 OCH_3), 72.3 (N—*C*=C), 112.3 (O—C=*C*), 158.9 and 173.8 (2 O—*C*=C), 163.4 and 169.6 (2 C=O ester), 195.2 (C=O). MS (EI, 70 eV): *m*/*z* (%) = 391 (M$^+$, 6), 333 (100), 251 (44), 218 (64), 52 (25). Anal. Calcd. for $C_{21}H_{29}NO_6$ (391.47): C, 64.43; H, 7.47; N, 3.58%. Found: C, 64.4; H, 7.5; N, 3.9%.

Diethyl 2-(cyclohexylamino)-5-oxo-7,7-dimethyl 5,6,7,8-tetrahydro-4H-chromene-3,4-dicarboxylate (4d). Light yellow oil (0.302 g, 0.72%). IR (KBr) (ν_{max} /cm^{-1}): 3228 (N—H), 1720, and 1680 (C=O), 1610 (C=C). ^{1}H NMR ($CDCl_3$): δ = 1.12 and 1.16 (6 H, 2 s, 2 CMe_2), 1.17 and 1.25 (6 H, 2 t, $^3J_{HH}$ = 7.5 Hz, 2 CH_3), 1.20–1.90 (10 H, m, 5 CH_2), 2.29 and 2.42 (4 H, 2 s, 2 CH_2), 3.61 (1 H, m, NCH), 4.10 and 4.19 (4 H, 2 q, $^3J_{HH}$ = 7.5 Hz, 2 OCH_2), 4.50 (1 H, s, CH), 8.60 (1 H, d, $^3J_{HH}$ = 7.4 Hz, NH). ^{13}C NMR ($CDCl_3$): δ = 14.2 and 14.6 (2 CH_3), 24.4, 25.5 and 33.8 (5 CH_2), 27.2 and 29.4 (C*Me*$_2$), 32.5 (*C*M_2), 34.4 (CH), 40.9 and 50.6 (2 CH_2), 49.9 (N—CH), 59.7 and 61.1 (2 OCH_2), 72.9 (N—*C*=C), 112.6 (O—C=*C*), 159.4 and 173.8 (2 O—*C*=C), 163.2 and 169.6 (2 C=O ester), 195.2 (C=O). MS (EI, 70 eV): *m*/*z* (%) = 419 (M$^+$, 4), 347 (100), 264 (75), 83 (25). Anal. Calcd. for $C_{23}H_{33}NO_6$ (419.51): C, 65.85; H, 7.93; N, 3.34%. Found: C, 65.9; H, 7.9; N, 3.3%.

Dimethyl 7-(cyclohexylamino)-1,3-dimethyl-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-5,6-dicarboxylate (4e). Yellow oil (0.346 g, 85%). IR (KBr) (ν_{max} /cm^{-1}): 3370 (N—H), 1741 and 1681 (C=O), 1537 (C=C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.11–2.10 (10 H, m, 5 CH_2), 3.34 and 3.41 (6 H, 2 s, 2 NCH_3), 3.65 (1 H, br m, NCH); 3.70 and 3.79 (6 H, 2 s, 2 OCH_3), 4.59 (1 H, s, CH), 8.60 (1 H, br d, $^3J_{HH}$ = 5.7 Hz, NH). ^{13}C NMR ($CDCl_3$): δ = 24.1, 25.2 and 33.5 (5 CH_2), 28.4 and 29.6 (2 N—CH_3), 35.3 (CH), 50.1 (HN—CH), 51.5 and 52.1 (2 OCH_3), 72.2 (N—C=*C*), 88.9 (O—C=*C*), 150.1 and 151.9 (2 C=O), 151.9 and 174.0 (2 O—*C*=C), 161.2 and 169.5 (2 C=O ester),. MS (EI, 70 eV): *m*/*z* (%) = 407 (M$^+$, 12), 348 (100), 324 (65), 316 (50), 83 (35), 59 (46). Anal. Calcd. for $C_{19}H_{25}N_3O_7$ (407.42): C, 56.01; H, 6.18; N, 10.31%; Found: C, 56.1; H, 6.2; N, 10.2.

Diethyl 7-(cyclohexylamino)-1,3-dimethyl-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-5,6-dicarboxylate (4f). Yellow oil (0.382 g, 88%). IR (KBr) (ν_{max} /cm^{-1}): 3375 (N—H), 1697 (C=O), 1541 (C=C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.10 and 1.12 (6 H, 2 t, $^3J_{HH}$ = 7.5 Hz, 2 CH_3), 1.20–2.94 (10 H, m, 5 CH_2), 3.34 and 3.42 (6 H, 2 s, 2 NCH_3), 3.65 (1 H, br m, NCH), 4.10 and 4.15 (4 H, 2 q, $^3J_{HH}$ = 7.5 Hz, 2 OCH_2), 4.55(1 H, s, CH), 8.70 (1 H, br d, $^3J_{HH}$ = 5.6 Hz, NH). ^{13}C NMR ($CDCl_3$): δ = 13.1 and 14.2 (2 CH_3), 24.2, 25.1 and 32.9 (5 CH_2), 28.9 and 33.1 (2 N—CH_3), 33.9 (CH), 54.1 (HN—CH), 59.1 and 60.0 (2 OCH_2), 73.1 (N—C=*C*), 88.7 (O—C=*C*), 150.2 and 151.9 (2 C=O), 157.9 and 171.5 (2 O—*C*=C), 161.2 and 169.5 (2 C=O ester),. MS (EI, 70 eV): *m*/*z* (%) = 435 (M^+, 5), 352 (100), 337 (65), 73 (50). Anal. Calcd. for $C_{21}H_{29}N_3O_7$ (435.47): C, 57.92; H, 6.71; N, 9.65%; Found: C, 57.9; H, 6.8; N, 9.7.

Dimethyl 2-(cyclohexylamino)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3,4-dicarboxylate (4g). Yellow paste (0.327 g, 0.90%). IR (KBr) (ν_{max} /cm^{-1}): 3405 (N—H), 1735, and 1686 (C=O), 1603 (C=C). ^{1}H NMR ($CDCl_3$): δ = 1.18–2.10 (10 H, m, 5 CH_2), 2.26–2.59 (4 H, m, 3 CH_2), 3.64 and 3.68 (6 H, 2 s, 2 OCH_3), 3.70 (1 H, m, NCH), 4.48 (1 H, s, CH), 8.57 (1 H, d, $^3J_{HH}$ = 7.2 Hz, NH). ^{13}C NMR ($CDCl_3$): δ = 20.2, 24.4, 25.5 33.6, 33.7 and 36.2 (8 CH_2), 34.4 (CH), 49.9 (N—CH), 50.5 and 52.2 (2 OCH_3), 77.1 (N—*C*=C), 112.9 (O—C=*C*), 158.1 and 173.8 (2 O—*C*=C), 164.0 and 169.5 (2 C=O ester), 196.1 (C=O). MS (EI, 70 eV): *m*/*z* (%) = 363 (M^+, 10), 331 (16), 305 (28), 280 (60), 190 (100), 43 (35). Anal. Calcd. for $C_{19}H_{25}NO_6$ (363.40): C, 62.80; H, 6.93; N, 3.85%; Found: C, 62.8; H, 6.9; N, 3.9.

Diethyl 2-(cyclohexylamino)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3,4-dicarboxylate (4h). Yellow oil (0.313 g, 0.80%), mp 140–142°C. IR (KBr) (ν_{max} /cm^{-1}): 3428, (N—H), 1726 and 1761 (C=O), 1182 (C—O). ^{1}H NMR ($CDCl_3$): δ = 1.17 and 1.25 (6 H, 2 t, $^3J_{HH}$ = 7.5 Hz, 2 CH_3), 1.20–1.92 (10 H, m, 5 CH_2), 2.29–2.69 (6 H, m, 6 CH_2), 3.69 (1 H, m, NCH), 4.15 and 4.21 (4 H, 2 q, $^3J_{HH}$ = 7.5 Hz, 2 OCH_2), 4.42 (1H, s, CH), 8.65 (1 H, d, $^3J_{HH}$ = 7.4 Hz, NH). ^{13}C NMR ($CDCl_3$): δ = 14.1, 14.2, 24.4, 25.5, 33.7 and 36.5 (8 CH_2), 27.2 and 29.4 (CMe_2), 32.5 (*C*M_2), 36.3 (CH), 49.9 (N—CH), 59.3 and 60.2 (2 OCH_2), 72.2 (N—*C*=C), 113.1 (O—C=*C*), 158.2 and 173.8 (2 O—*C*=C), 164.0 and 169.6 (2 C=O ester), 196.1 (C=O). MS (EI, 70 eV): *m*/*z* (%) = 391 (M^+, 5), 362 (14), 308 (100), 190 (82), 83 (29). Anal. Calcd. for $C_{21}H_{29}N_3O_6$ (391.46): C, 64.43; H, 7.47; N, 3.58%; Found: C, 64.5; H, 7.5; N, 3.6

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