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Synthesis of fully substituted pyrano[2,3-*c*]pyrazole derivatives via a multicomponent reaction of isocyanides

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ABSTRACT

The three-component reaction of the zwitterions generated from dialkyl acetylenedicarboxylate and isocyanides with 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one is described. The reaction afforded the corresponding special type of fully substituted pyrano[2,3-*c*]pyrazole derivatives in good yields without using any catalyst and activation.

1. Introduction

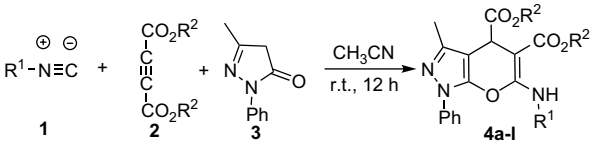
Multicomponent reactions (MCRs) are special types of synthetically useful organic reactions in which three or more different starting materials react to a final product in an onepot procedure.[1] Such reactions are atom-efficient processes by incorporating the essential parts of the starting materials into the final product. MCRs are powerful tools in the modern drug discovery process and allow the fast, automated, and high-throughput generation of organic compounds.[2] In the past years the pharmaceutical industry has focused more and more on diversity-oriented and biased combinatorial libraries.[3,4] Furthermore, the discovery of novel MCRs can be considered as an interesting topic for academic research that also satisfies a practical interest of applied science.[5–9]

Dihydropyrano[2,3-*c*]pyrazoles play an essential role in biologically active compounds and therefore represent an interesting template for medicinal chemistry. They have been widely used as medicine intermediates due to their useful biological and pharmacological properties, such as antimicrobial,[10] insecticidal,[11] and anti-inflammatory.[12] Furthermore dihydropyrano[2,3-*c*]pyrazoles showed molluscicidal activity[13,14] and was identified as a screening hit for Chk1 kinase inhibitor.[15]

Over the last years, the chemistry of dihydropyrano[2,3-*c*]-pyrazoles has received great interest. The first approach to synthesize of these substances was undertaken by Otto,[16] in which he initiated the reaction sequence by the base-catalyzed cyclization of 4-aryliden-5-pyrazolone. In a further report, this same group showed that weak bases can also be used for a Michael-type cyclization.[17]

Extending the work of Otto, Klokol and colleagues performed the direct conversion of 3-methyl-3-pyrazolin-5-one with malononitrile in the presence of a weak base.[18] Recent methods for the synthesis of 1,4-dihydropyrano[2,3-*c*]pyrazoles include synthesis based on the procedure of Klokol,[19] water or ethanol media,[20–25] under microwave irradiation,[26] and under solvent-free conditions.[27]

As part of our continuing interest in the development of new synthetic methods in heterocyclic chemistry and our interest in isocyanide based multicomponent reactions,[28–33] herein we describe an efficient synthesis of fully substituted pyrano[2,3-*c*]pyrazoles **4** via the reaction of an isocyanide **1** with an dialkyl acetylenedicarboxylate **2** and 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one **3** in high yields without using any catalyst at ambient temperature (Scheme 1).



Scheme 1. Synthesis of pyrano[2,3-*c*]pyrazoles via a three-component reaction.

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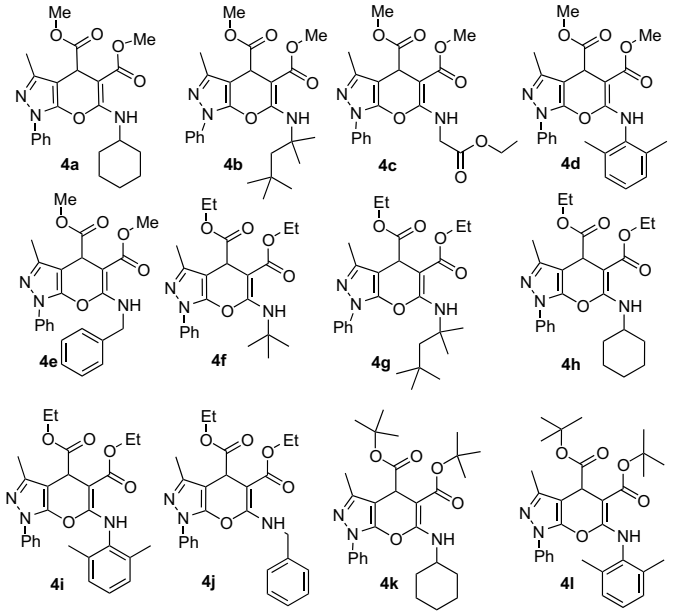
2. Results and discussion

As indicated in Table 1, isocyanides **1** with dialkyl acetylenedicarboxylate **2** and 1-phenyl-1*H*-pyrazol-5(4*H*)-one **3** undergo a smooth 1:1:1 addition reaction in CH_3CN at ambient temperature to produce pyrano[2,3-*c*]pyrazole **4**. The structures of the products were deduced from their IR, mass, ^1H NMR, and ^{13}C NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at the appropriate *m*/*z* values. The ^1H NMR spectrum of **4a** consisted of a multiplet for the cyclohexyl ring (δ=1.28–2.15 ppm), a singlet for methyl group (δ=2.30 ppm), multiplet for the NH–C*H* cyclohexyl proton (δ=3.62 ppm), two singlet for methoxy groups (δ=3.66 ppm and δ=3.70 ppm), a singlet for the C*H*–CO_2Me (δ=4.57 ppm), a triplet for the aromatic protons (δ=7.27 ppm, $^3J_{HH}$=7.2 Hz), a triplet for the aromatic proton (δ=7.42 ppm, $^3J_{HH}$=7.3 Hz), a doublet for the aromatic protons (δ=7.55 ppm, $^3J_{HH}$=7.4 Hz), and a broad singlet for NH (δ=8.87 ppm) protons. The ^1H decoupled ^{13}C NMR spectrum of **4a** showed 21 distinct resonances, partial assignment of these resonances is given in the Experimental section.

The reaction did not require any optimization, and we explored the use of various alkyl and aryl isocyanides with phenyl-1*H*-pyrazol-5(4*H*)-one in CH_3CN at ambient temperature, which led to the formation of the corresponding pyrano[2,3-*c*]pyrazole derivatives in high yields.

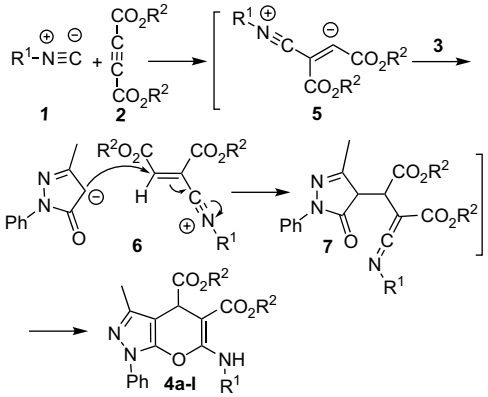
The reaction proceeds under mild conditions and is compatible with a wide range of functional groups. Owing to the great diversity of substitution patterns, this reaction may be used in the production of combinatorial libraries (Table 1).

Table 1
Synthesis of pyrano[2,3-*c*]pyrazole derivatives



Entry	R^1	R^2	Product	Yield (%)
1	Cyclohexyl	Me	**4a**	79
2	1,1,3,3-Tetramethyl-butyl	Me	**4b**	75
3	Ethoxycarbonylmethyl	Me	**4c**	58
4	2,6-Dimethyl-phenyl	Me	**4d**	64
5	Benzyl	Me	**4e**	70
6	*tert*-Butyl	Et	**4f**	75
7	1,1,3,3-Tetramethyl-butyl	Et	**4g**	72
8	Cyclohexyl	Et	**4h**	74
9	2,6-Dimethyl-phenyl	Et	**4i**	76
10	Benzyl	Et	**4j**	69
11	Cyclohexyl	^{t}Bu	**4k**	74
12	2,6-Dimethyl-phenyl	^{t}Bu	**4l**	58

Although the mechanism of this reaction has not been established experimentally, the formation of these heterocycles can be rationalized by initial Michael-type vinylisonitrilium cation **5**.[28,34–36] Then, the positively charged ion might be attacked by the anion of the phenyl-1*H*-pyrazol-5(4*H*)-one to give the keteneimine **7**. Such an addition product may isomerize under the reaction conditions employed to produce the fused heterocyclic system **4a–l** (Scheme 2).



Scheme 2. Proposed mechanism.

3. Conclusion

In conclusion, we have developed a new and efficient approach to the synthesis of fully substituted pyrano[2,3-*c*]pyrazole derivatives from various isocyanides and dialkyl acetylenedicarboxylates in the presence of phenyl-1*H*-pyrazol-5(4*H*)-one in absence of any catalyst. The reaction has been shown to display relatively good functional group tolerance and is high yielding and product isolation is very straightforward. We hope that this approach may be of value to others seeking novel synthetic fragments with unique properties for medicinal chemistry.

4. Experimental

4.1. General

Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. 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. ^1H and ^{13}C NMR spectra were recorded on a BRUKER DRX-300 AVANCE spectrometer at 300.13 and 75.47 MHz. NMR spectra were obtained on solution in $CDCl_3$ using TMS as internal standard. The chemicals used in this work were purchased from Merck and Fluka Chemical Companies.

*4.1.1. Typical procedure for preparation of dimethyl 6-(cyclohexylamino)-1,4-dihydro-3-methyl-1-phenylpyrano[2,3-c]pyrazole-4,5-dicarboxylate (**4a**)*

To a magnetically stirred solution of phenyl-1*H*-pyrazol-5(4*H*)-one (0.17 g, 1.0 mmol) and dimethyl acetylenedicarboxylate (0.14 g, 1.0 mmol) in CH_3CN (10 mL) was added dropwise a solution of cyclohexyl isocyanide (0.11 g, 1 mmol) in CH_3CN (2 mL) at room temperature over 10 min. The mixture was finally stirred for 12 h. The solvent was removed under vacuum and the residue was crystallized from *n*-hexane/dichloromethane (2:1) mixture and washed with ether (3×5 mL) and the product **4a** was obtained. White crystals (0.34 g, yield 79%). Mp 136–138 °C. IR (KBr) (ν_{max}/cm^{-1}): 2937, 2856,

1743, 1681, 1633. MS, *m*/*z* (%): 426 (M^++1, 10), 372 (25), 354 (100), 289 (90), 252 (30), 185 (10), 77 (20), 57 (30). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) 1.28–2.15 (10H, m, $5CH_2$ of cyclohexyl), 2.30 (3H, s, CH_3), 3.62 (1H, br s, C*H*–NH), 3.66 (3H, s, O–CH_3), 3.70 (3H, s, O–CH_3), 4.57 (1H, s, C*H*–CO_2Me), 7.27 (1H, t, $^3J_{HH}$=7.2 Hz, arom), 7.42 (2H, t, $^3J_{HH}$=7.3 Hz, arom), 7.55 (2H, d, $^3J_{HH}$=7.4 Hz, arom), 8.87 (1H, br s, CH–N*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 12.82 (CH_3), 24.63, 24.71, 25.38, 33.51, 33.78 (C-cyclohexyl), 37.22 (*C*H–CO_2Me), 50.77 (CH–NH), 51.15, 52.17 (2O–CH_3), 71.67, 95.11, 120.50, 126.46, 129.15, 137.67, 144.28, 146.41, 159.68 (C-alkene, C–Ar), 170.05, 173.68 (2C=O). Anal. Calcd for $C_{23}H_{27}N_3O_5$: C, 64.93; H, 6.40; N, 9.88%. Found: C, 64.97; H, 6.33; N, 9.93%.

4.1.2. Dimethyl 6-(1,1,3,3-tetramethylpentylamino)-1,4-dihydro-3-methyl-1-phenylpyrano[2,3-c]pyrazole-4,5-dicarboxylate (**4b**)

White crystals (0.34 g, yield 75%). Mp 143–146 °C. IR (KBr) (ν_{max}/cm^{-1}): 2951, 2867, 1748, 1670, 1637, 1603. MS, *m*/*z* (%): 456 (M^++1, 5), 396 (50), 344 (30), 284 (100), 252 (40), 77 (35), 55 (65), 57 (70). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) 0.88 (9H, s, $C(CH_3)_3$), 1.34 (3H, s, CH_3), 1.36 (3H, s, CH_3), 1.61 (2H, s, CH_2), 2.29 (3H, s, CH_3), 3.67 (3H, s, O–CH_3), 3.68 (3H, s, O–CH_3), 4.58 (1H, s, CH–CO_2Me), 7.31 (1H, t, $^3J_{HH}$=7.2 Hz, arom), 7.42 (2H, t, $^3J_{HH}$=7.8 Hz, arom), 7.55 (2H, d, $^3J_{HH}$=7.9 Hz, arom), 9.19 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 12.82 (CH_3), 30.94, 31.14 ($2CH_3$), 31.24 ($C(CH_3)_3$), 31.48 (CH_2), 37.17 (CH–CO_2Me), 51.15, 52.10 (2O–CH_3), 52.71 (C–NH), 56.30, 72.38, 94.96, 123.11, 127.47, 129.08, 137.09, 144.34, 146.39, 161.00 (C-alkene, C–Ar), 170.25, 173.70 (2C=O). Anal. Calcd for $C_{25}H_{33}N_3O_5$: C, 65.91; H, 7.30; N, 9.22%. Found: C, 65.83; H, 7.26; N, 9.25%.

4.1.3. Dimethyl 6-((ethoxycarbonyl)methylamino)-1,4-dihydro-1-phenylpyrano[2,3-c]pyrazole-4,5-dicarboxylate (**4c**)

White crystals (0.25 g, yield 58%). Mp 140–143 °C. IR (KBr) (ν_{max}/cm^{-1}): 2989, 2949, 1734, 1680, 1636. MS, *m*/*z* (%): 430 (M^++1, 3), 292 (100), 210 (65), 178 (70), 88 (25), 59 (30), 55 (65), 41 (60). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) 1.21 (3H, t, s, $^3J_{HH}$=7.1 Hz, CH_2CH_3), 2.31 (3H, s, CH_3), 3.71 (3H, s, O–CH_3), 3.72 (3H, s, O–CH_3), 4.01–4.20 (4H, m, CH_2CH_3, HNCH_2), 4.60 (1H, s, C*H*–CO_2Me), 7.28 (1H, t, $^3J_{HH}$=7.2 Hz, arom), 7.43 (2H, t, $^3J_{HH}$=7.9 Hz, arom), 7.56 (2H, d, $^3J_{HH}$=7.7 Hz, arom), 9.15 (1H, br s, CH_2–N*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 12.91, 14.09 ($2CH_3$), 37.28 (*C*H–CO_2Me), 43.09 (CH_2–NH), 51.46, 52.26 (2O–CH_3), 61.67 (OCH_2CH_3), 74.19, 95.18, 120.89, 126.64, 129.24, 137.49, 143.90, 146.42, 159.63 (C-alkene, C–Ar), 169.63, 169.74, 173.28 (3C=O). Anal. Calcd for $C_{21}H_{23}N_3O_7$: C, 58.74; H, 5.40; N, 9.79%. Found: C, 58.64; H, 5.33; N, 9.73%.

4.1.4. Dimethyl 6-(2,6-dimethylphenylamino)-1,4-dihydro-3-methyl-1-phenylpyrano[2,3-c]pyrazole-4,5-dicarboxylate (**4d**)

White crystals (0.29 g, 64%). Mp 193–195 °C. IR (KBr) (ν_{max}/cm^{-1}): 2971, 2898, 1734, 1676, 1630. MS, *m*/*z* (%): 448 (M^++1, 3), 447 (M^+, 2), 388 (100), 356 (20), 273 (10), 105 (5), 77 (25). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) 2.21 (3H, s, CH_3), 2.32 (3H, s, CH_3), 2.34 (3H, s, CH_3), 3.75 (3H, s, O–CH_3), 3.80 (3H, s, O–CH_3), 4.68 (1H, s, CH–CO_2Me), 7.07–7.21 (8H, m, arom), 10.02 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 12.93, 18.34, 18.43 ($3CH_3$), 37.33 (CH–CO_2Me), 51.50, 52.31 (2O–CH_3), 73.74, 95.25, 118.23, 125.62, 127.51, 128.21, 128.90, 134.26, 137.57, 144.32, 146.15, 159.38 (C-alkene, C–Ar), 170.11, 173.32 (2C=O). Anal. Calcd for $C_{25}H_{25}N_3O_5$: C, 67.10; H, 5.63; N, 9.39%. Found: C, 66.53; H, 5.53; N, 9.34%.

4.1.5. Dimethyl 6-(benzylamino)-1,4-dihydro-3-methyl-1-phenylpyrano[2,3-c]pyrazole-4,5-dicarboxylate (**4e**)

White crystals (0.30 g, 70%). Mp 174–176 °C. IR (KBr) (ν_{max}/cm^{-1}): 2944, 2891, 1738, 1680, 1637. MS, *m*/*z* (%): 434 (M^++1, 5), 433 (M^+, 2), 374 (80), 251 (10), 185 (10), 91 (100), 77 (20), 65 (10). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) 2.31 (3H, s, CH_3), 3.73 (3H, s, O–CH_3), 3.82 (3H, s, O–CH_3), 4.55–4.62 (3H, m, CH_2 of benzyl, CH–CO_2Me), 7.29–7.43 (10H, m, arom), 9.38 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 12.92 (CH_3), 37.27 (CH–CO_2Me), 45.04 (CH_2 of benzyl), 51.34, 52.25 (2O–CH_3), 73.01, 95.08, 121.03, 126.60, 126.64, 127.53, 128.80, 129.19, 137.42, 137.98, 144.06, 146.33, 160.18 (C-alkene, C–Ar), 170.06, 173.54 (2C=O). Anal. Calcd for $C_{24}H_{23}N_3O_5$: C, 66.50; H, 5.35; N, 9.69%. Found: C, 66.16; H, 5.39; N, 9.54%.

4.1.6. Diethyl 6-(tert-butylamino)-1,4-dihydro-3-methyl-1-phenylpyrano[2,3-c]pyrazole-4,5-dicarboxylate (**4f**)

White crystals (0.32 g, 75%). Mp 137–140 °C. IR (KBr) (ν_{max}/cm^{-1}): 2935, 2847, 1783, 1745, 1673. MS, *m*/*z* (%): 427 (M^+, 2), 426 (M^+−1, 5), 366 (100), 252 (30), 185 (10), 77 (20), 55 (20). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H=1.21–1.29 (6H, m, $2CH_3$), 1.33 (9H, s, $C(CH_3)_3$), 2.31 (3H, s, CH_3), 4.05–4.23 (4H, m, $2OCH_2$), 4.56 (1H, s, CH–CO_2Et), 7.29 (1H, t, $^3J_{HH}$=7.1 Hz, arom), 7.41 (2H, t, $^3J_{HH}$=8.0 Hz, arom), 7.57 (2H, d, $^3J_{HH}$=7.7 Hz, arom), 9.15 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C=12.99, 14.28, 14.39 ($3CH_3$), 30.29 ($C(CH_3)_3$), 37.40 (CH–CO_2Et), 52.61 ($C(CH_3)_3$), 59.68, 60.94 ($2OCH_2$), 72.87, 94.94, 122.72, 127.26, 129.03, 137.19, 144.35, 146.35, 169.99 (C-alkene, C–Ar), 169.86, 173.46 (2C=O). Anal. Calcd for $C_{23}H_{29}N_3O_5$: C, 64.62; H, 6.84; N, 9.83%. Found: C, 64.58; H, 6.80; N, 9.77%.

4.1.7. Diethyl 6-(1,1,3,3-tetramethylpentylamino)-1,4-dihydro-3-methyl-1-phenylpyrano[2,3-c]pyrazole-4,5-dicarboxylate (**4g**)

White crystals (0.35 g, 72%). Mp 144–147 °C. IR (KBr) (ν_{max}/cm^{-1}): 2951, 2784, 1738, 1673, 1601. MS, *m*/*z* (%): 411 (M^+−72, 10), 410 (60), 372 (15), 298 (90), 252 (25), 215 (60), 199 (95), 174 (70), 91 (45), 77 (100), 57 (50). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) 0.90 (9H, s, $C(CH_3)_3$), 1.21–1.28 (6H, m, $2OCH_2CH_3$), 1.34 (3H, s, CH_3), 1.40 (3H, s, CH_3), 1.60 (1H, AB-q, $^2J_{HH}$=8.2 Hz, CH_AH_B), 1.65 (1H, AB-q, $^2J_{HH}$=8.2 Hz, CH_AH_B), 2.32 (3H, s, CH_3), 4.11–4.18 (4H, m, $2OCH_2CH_3$), 4.57 (CH–CO_2Et), 7.27–7.58 (5H, m, arom), 9.20 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 12.97, 14.27, 14.40 ($3CH_3$), 31.03, 31.14 ($2CH_3$), 31.27 ($C(CH_3)_3$), 31.50 (CH_2), 37.42 (*C*H–CO_2Et), 52.71 ($C(CH_3)_3$), 56.22 (C–NH), 59.62, 60.90 (2O–CH_2), 72.57, 95.01, 123.12, 127.43, 129.07, 137.13, 144.38, 146.43, 160.89 (C-alkene, C–Ar), 169.93, 173.44 (2C=O). Anal. Calcd for $C_{27}H_{37}N_3O_5$: C, 67.06; H, 7.71; N, 8.69%. Found: C, 68.91; H, 6.96; N, 11.53%.

4.1.8. Diethyl 6-(cyclohexylamino)-1,4-dihydro-3-methyl-1-phenylpyrano[2,3-c]pyrazole-4,5-dicarboxylate (**4h**)

White crystals (0.41 g, 74%). Mp 139–141 °C. IR (KBr) (ν_{max}/cm^{-1}): 2937, 2856, 1743, 1681, 1633. MS, *m*/*z* (%): 553 (M^++1, 3), 292 (100), 210 (65), 178 (70), 88 (25), 59 (30), 55 (65), 41 (60). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) 1.22–2.29 (16H, m, $5CH_2$ of cyclohexyl, $2OCH_2CH_3$), 2.33 (3H, s, CH_3), 3.66 (1H, br s, CH–NH), 4.09–4.24 (4H, m, $2OCH_2CH_3$), 4.58 (1H, s, CH–CO_2Me), 7.26–7.68 (5H, m, arom), 8.88 (1H, d, ^3J=6.5 Hz, CH–NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 13.08, 14.31, 14.44 ($3CH_3$), 24.68, 24.75, 25.51, 33.54, 33.83 (C-cyclohexyl), 37.43 (CH–CO_2Et), 50.75 (CH–NH), 59.63, 60.99 ($2OCH_2CH_3$), 71.86, 95.19, 120.53, 126.44, 129.15, 137.71, 144.35, 146.42, 159.62 (C-alkene, C–Ar), 169.73, 173.46 (2C=O). Anal. Calcd for $C_{25}H_{31}N_3O_5$: C, 66.21; H, 6.89; N, 9.27%. Found: C, 65.69; H, 6.81; N, 9.13%.

4.1.9. Diethyl 6-(2,6-dimethylphenylamino)-1,4-dihydro-3-methyl-1-phenylpyrano[2,3-c]pyrazole-4,5-dicarboxylate (**4i**)

White crystals (0.36 g, 76%). Mp 166–168 °C. IR (KBr) (ν_{max}/cm^{-1}): 2975, 2897, 1729, 1677, 1644. MS, *m*/*z* (%): 476 (M^++1, 5), 475 (M^+, 3), 402 (100), 356 (50), 302 (20), 185 (5), 77 (20). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) 1.28–1.34 (6H, m, $2OCH_2CH_3$), 2.15 (3H, s, CH_3), 2.21 (3H, s, CH_3), 3.34 (3H, s, CH_3), 4.14–4.31 (4H, m, $2OCH_2CH_3$), 4.67 (1H, s, CH–CO_2Et), 7.07–7.24 (8H, m, arom), 10.04 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 13.05, 14.27, 14.41, 18.35 ($4CH_3$), 37.56 (CH–CO_2Et), 60.02, 61.09 ($2OCH_2CH_3$), 73.97, 95.30, 118.69, 125.55, 127.43, 128.23, 128.87, 134.39, 136.44, 136.82, 137.64, 144.35, 146.13, 159.25 (C-alkene, C–Ar), 169.75,

172.99 (2C=O). Anal. Calcd for $C_{27}H_{29}N_3O_5$: C, 68.19; H, 6.15; N, 8.84%. Found: C, 67.83; H, 6.07; N, 8.82%.

*4.1.10. Diethyl 6-(benzylamino)-1,4-dihydro-3-methyl-1-phenylpyrano[2,3-c]pyrazole-4,5-dicarboxylate (**4j**)*

White crystals (0.32 g, 69%). Mp 128–129 °C. IR (KBr) (ν_{max}/cm^{-1}): 2980, 2952, 2929, 1734, 1677, 1639. MS, *m*/*z* (%): 461 (M^+−86, 10), 410 (60), 372 (15), 298 (90), 252 (25), 215 (60), 199 (95), 174 (70), 91 (45), 77 (100), 57 (50). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) 1.26–1.34 (6H, m, 2OCH$_2$C*H*$_3$), 2.33 (3H, s, CH$_3$), 4.14–4.24 (4H, m, 2OC*H*$_2$CH$_3$), 4.24–4.61 (3H, m, CH$_2$ of benzyl, C*H*–CO$_2$Me), 7.27–7.43 (10H, m, arom), 9.32 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 13.05, 14.31, 14.40 (3CH$_3$), 37.47 (*C*H–CO$_2$Me), 45.00 (CH$_2$ of benzyl), 59.86, 61.07 (2O*C*H$_2$CH$_3$), 73.20, 95.14, 121.01, 126.54, 126.62, 127.47, 128.78, 129.17, 137.46, 138.11, 144.10, 146.32, 160.09 (C-alkene, C–Ar), 169.74, 173.29 (2C=O). Anal. Calcd for $C_{26}H_{27}N_3O_5$: C, 67.66; H, 5.90; N, 9.10%. Found: C, 67.00; H, 5.81; N, 9.06%.

*4.1.11. Di-tert-butyl 6-(cyclohexylamino)-1,4-dihydro-3-methyl-1-phenylpyrano[2,3-c]pyrazole-4,5-dicarboxylate (**4k**)*

White crystals (0.38 g, 74%). Mp 155–158 °C. IR (KBr) (ν_{max}/cm^{-1}): 2978, 2952, 2854, 1740, 1673, 1636. MS, *m*/*z* (%): 510 (M^+−1, 5), 408 (25), 352 (100), 252 (20), 226 (15), 77 (20), 57 (45). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) 1.27–2.04 (28H, m, 5CH$_2$ of cyclohexyl, 2OC(CH$_3$)$_3$), 2.36 (3H, s, CH$_3$), 3.59 (br s,1H, C*H*–NH), 4.40 (1H, s, C*H*–CO$_2$^{t}Bu), 7.23–7.70 (5H, m, arom), 8.79 (1H, br s, CH–N*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 13.22 (CH$_3$), 24.92, 24.99, 25.45, 33.76, 33.96 (C-cyclohexyl), 28.12, 28.56 (2OC(*C*H$_3$)$_3$), 38.61 (*C*H–CO$_2$^{t}Bu), 50.86 (CH–NH), 73.41, 79.55, 80.76 (2O*C*(CH$_3$)$_3$), 95.88, 120.31, 126.22, 129.09, 137.85, 144.53, 146.22, 159.47 (C-alkene, C–Ar), 169.52, 172.73 (2C=O). Anal. Calcd for $C_{29}H_{39}N_3O_5$: C, 68.34; H, 7.71; N, 8.25%. Found: C, 68.07; H, 7.65; N, 8.09%.

*4.1.12. Di-tert-butyl 6-(2,6-dimethylphenylamino)-1,4-dihydro-3-methyl-1-phenylpyrano[2,3-c]pyrazole-4,5-dicarboxylate (**4l**)*

White crystals (0.31 g, 58%). Mp 166–168 °C. IR (KBr) (ν_{max}/cm^{-1}): 2975, 2926, 1738, 1676, 1635. MS, *m*/*z* (%): 531 (M^++1, 2), 373 (M^+, 3), 314 (100), 282 (20), 254 (20), 226 (10), 143 (10), 111 (90), 77 (20), 59 (25), 39 (60). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) 1.48 (9H, s, OC(CH$_3$)$_3$), 1.56 (9H, s, OC(CH$_3$)$_3$), 2.20 (3H, s, CH$_3$), 2.35 (3H, s, CH$_3$), 2.37 (3H, s, CH$_3$), 4.50 (1H, s, CH–CO$_2$^{t}Bu), 7.08–7.18 (8H, m, arom), 10.03 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 13.17, 18.36, 18.52 (3CH$_3$), 28.07, 28.54 (2OC(CH$_3$)$_3$), 39.01 (CH–CO$_2$^{t}Bu), 75.48 (C-alkene), 80.28, 80.78 (2OC(CH$_3$)$_3$), 95.82, 118.55, 125.38, 127.21, 128.13, 128.85, 134.72, 136.48, 136.88, 137.79, 144.48, 146.07, 158.94 (C-alkene, C–Ar), 169.58, 172.03 (2C=O). Anal. Calcd for $C_{31}H_{37}N_3O_5$: C, 70.03; H, 7.01; N, 7.90%. Found: C, 69.81; H, 6.93; N, 7.63%.

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Supplementary data

Experimental procedures, IR, Mass, ^{1}H NMR, and ^{13}C NMR spectra and also elemental analysis for compounds **4a**–**l** are provided. This material is available via the Internet at http://www.elsevier.com. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.02.035.

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