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An isocyanide-based three-component reaction: synthesis of fully substituted *N*-alkyl-2-triphenylphosphoranylidene glutarimides

Ahmad Shaabani,[a,*] Ebrahim Soleimani,[a] Hamid Reza Khavasi,[a] Ralf-Dieter Hoffmann,[b] Ute Ch. Rodewald[b] and Rainer Pöttgen[b]

[a]*Department of Chemistry, Shahid Beheshti University, PO Box 19396-4716, Tehran, Iran*
[b]*Institut für Anorganische und Analytische Chemie, Universität Münster, Corrensstrasse 30, D-48149 Münster, Germany*

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Abstract—A three-component condensation reaction between an isocyanide, an electron-deficient acetylenic ester and (ethoxycarbonylmethyl)triphenylphosphonium bromide efficiently provides fully substituted *N*-alkyl-2-triphenylphosphoranylidene glutarimides in a one-pot reaction without any activation or modification.

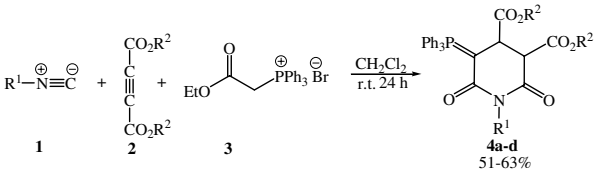
1. Introduction

Piperidine-2,6-diones (glutarimides, cyclic imides) have various biological activities[1] and the 2,6-piperidinedione moiety constitutes an important substructure in several new anticancer agents which have recently been introduced into experimental chemotherapy.[2,3] Furthermore, they have been used as precursors in the synthesis of a variety of heterocyclic compounds.[4] Therefore, the synthesis of piperidine-2,6-dione derivatives has attracted considerable attention and several methods have been reported in the literature,[5–13] most of which relied on multi-step reactions using harsh reaction conditions.

Due to the atom economy, convergent character, and simplicity of one-pot procedures, multi-component condensation reactions (MCRs) have an advantageous position among other reactions. The discovery and development of novel MCRs is receiving growing interest from industrial chemistry research groups and represents a new challenge for organic chemists and to the basic understanding of organic chemistry itself.[14]

Continuing our interest in isocyanide-based multi-component reactions,[15] herein we report on a hitherto unknown three-component reaction, which, starting from simple and readily available precursors affords fully functionalized *N*-alkyl-2-triphenylphosphoranylidene glutarimides (Scheme 1).

The alkyl isocyanide **1** and dialkyl acetylenedicarboxylate **2** in the presence of (ethoxycarbonylmethyl) triphenylphosphonium bromide **3** undergo a smooth 1:1:1 addition reaction in dichloromethane at room temperature to produce *N*-alkyl-2-triphenylphosphoranylidene glutarimides **4**. The structures of the products were deduced from their IR, ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at the appropriate *m*/*z* values.



1 **2** **3** **4a-d** 51-63%

4	R^1	R^2	Yield (%)
a	Cyclohexyl	Me	63
b	Cyclohexyl	Et	61
c	Cyclohexyl	*t*-Bu	56
d	*t*-Bu	Et	51

Scheme 1.

Keywords: Glutarimide; Piperidine-2,6-dione; Isocyanide; Multi-component reactions.
* Corresponding author. Fax: +98 21 22403041; e-mail: a-shaabani@cc.sbu.ac.ir

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The ^{1}H NMR spectrum of **4b** consisted of two triplets for the methyl groups (OCH_2CH_3, $\delta = 1.07$ and 1.25 ppm), a multiplet for the cyclohexyl ring ($\delta = 1.15$–2.42 ppm), a doublet of doublets for P=C–CH ($\delta = 3.00$ ppm, $^3J_{HP} = 11.9$ Hz, $^3J_{HH} = 2.0$ Hz), a doublet of doublets for P=C–CH–CH ($\delta = 3.79$ ppm, $^4J_{HP} = 4.3$ Hz, $^3J_{HH} = 2.0$ Hz), a multiplet for the two methylene groups (OCH_2CH_3, $\delta = 3.98$–4.29 ppm), a triplet of triplets for the N–CH proton ($\delta = 4.47$ ppm, $^3J_{HH} = 11.8$ Hz, $^3J_{HH} = 3.3$ Hz) and the phenyl moieties gave rise to multiplets in the aromatic region of the spectrum ($\delta = 7.47$–7.66 ppm). The ^{1}H decoupled ^{13}C NMR spectrum of **4b** showed 29 distinct resonances (^{31}P coupled), partial assignment of these resonances is given in the experimental section. The ^{31}P NMR spectrum of **4b** exhibited a single peak at ($\delta = 20.19$ ppm). Finally, the structure of **4b** was confirmed unambiguously by single crystal X-ray analysis (Fig. 1).[16]

Although the mechanism of the reaction between the isocyanide and dialkyl acetylenedicarboxylate in the presence of CH acids has not yet been established experimentally, a possible explanation is proposed in Scheme 2. On the basis of the well established chemistry of isocyanides,[17–20] it is reasonable to assume that protonation of the 1:1 zwitterionic intermediate by the CH acid followed by quenching of the cationic center by the conjugate base of the CH acid can generate the ketenimine **6**.[15g] Such an addition product may eliminate EtBr and then isomerize under the reaction conditions to produce **4**.

To explore the scope and limitations of this reaction, we extended the procedure to various dialkyl acetylenedicarboxylates in the presence of cyclohexyl or *tert*-butyl isocyanide and (ethoxycarbonylmethyl)triphenylphosphonium bromide. Based on ^{1}H NMR and ^{13}C NMR spectra of the crude reactions, we found that only the 4-trans diastereoisomer was produced with dimethyl acetylenedicarboxylate and diethyl acetylenedicarboxylate, however, when di-*tert*-butyl acetylenedicarboxylate was used, both the 4-cis (37%) and 4-trans (63%) diastereoisomers were obtained (Scheme 3).

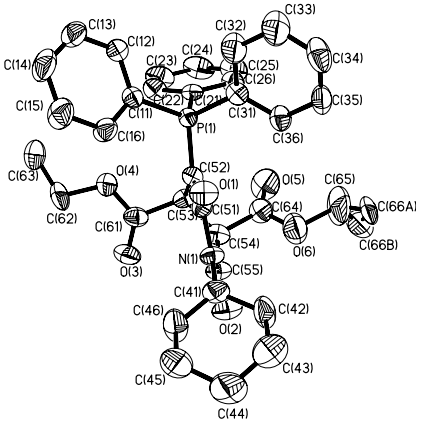
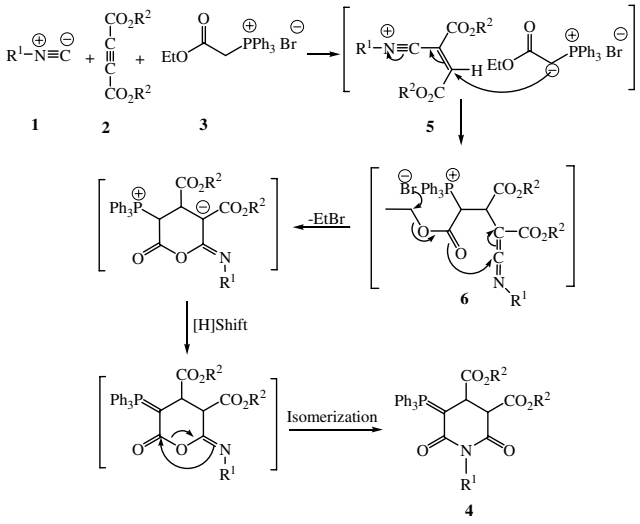
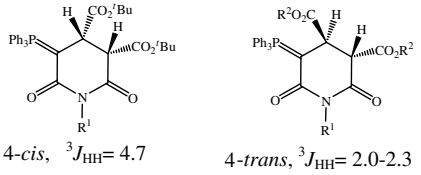


Figure 1. Single crystal X-ray structure of **4b**. The C-66 atoms show disorder.



Scheme 2.



Scheme 3.

In conclusion, we have introduced a three-component condensation reaction leading to fully functionalized *N*-alkyl-2-triphenylphosphoranylidene glutarimide derivatives which constitute an essential part of many natural products with antibacterial, antitumor or fungicidal activity from simple and readily available precursors under neutral conditions without any prior activation.

2. Experimental

2.1. Typical procedure for the preparation of 1-cyclohexyl-2,6-dioxo-5-(triphenyl-λ^*5^*-phosphanylidene)-piperidine-3,4-dicarboxylic acid dimethyl ester (4a)

To a magnetically stirred solution of (ethoxycarbonylmethyl)triphenylphosphonium bromide (0.43 g, 1.0 mmol) and dimethylacetylenedicarboxylate (0.14 g, 1.0 mmol) in CH_2Cl_2 (20 mL) was added, dropwise, a mixture of cyclohexyl isocyanide (0.11 g, 1 mmol) in CH_2Cl_2 (2 mL) at −10 °C over 10 min. The mixture was allowed to warm to room temperature and was stirred for 24 h. The solvent was removed under vacuum and the residue was crystallized from an EtOH/H_2O (1:2) mixture and washed with H_2O (3 × 5 mL). The product **4a** was obtained in the form of colorless crystals (0.36 g, yield 63%); mp 196–198 °C (dec). IR (KBr) (ν_{max}/cm^{-1}): 2920, 1731, 1680, 1589, 1431. MS, *m*/*z* (%): 571 (M^+, 4), 512 (100), 430 (20), 398 (15), 370 (12), 287 (12), 262 (34), 183 (66), 152 (17), 107 (48), 77 (37), 59 (53), 41 (75). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) 1.08–2.28 (10H, m, 5CH_2 of cyclo-

hexyl), 2.98 (1H, dd, $^3J_{HP} = 10.7$ Hz,$^3J_{HH} = 2.0$ Hz, P=C–CH), 3.47, 3.64 (6H, 2s, 2OCH$_3$), 3.76 (1H, d, $^3J_{HH} = 2.0$ Hz, P=C–CH–C*H*), 4.37 (1H, t, $^3J_{HH} = 12.0$ Hz, CH–N), 7.42–7.57 (15H, m, H–Ar of P(C$_6$H$_5$)$_3$). ^{13}C NMR (75 MHz, CDCl$_3$): δ_C (ppm) 25.44, 26.43, 26.57, 28.66, 29.85 (5CH$_2$ of cyclohexyl), 40.26 (d, $^2J_{PC} = 11.5$ Hz, P=C–*C*H), 42.82 (d, $^1J_{PC} = 135.7$ Hz, C=P), 51.96 (OCH$_3$), 52.39 (CH–N), 52.74 (OCH$_3$), 52.32 (d, $^3J_{PC} = 7.6$ Hz, P=C–CH–*C*H), 125.33 (d, $^1J_{PC} = 93.1$ Hz, C_{ipso} of P(C$_6$H$_5$)$_3$), 128.78 (d, $^3J_{PC} = 12.4$ Hz, C_{meta} of P(C$_6$H$_5$)$_3$), 132.25 (C_{para} of P(C$_6$H$_5$)$_3$), 133.67 (d, $^2J_{PC} = 10.0$ Hz, C_{ortho} of P(C$_6$H$_5$)$_3$), 166.95 (d, $^2J_{PC} = 13.0$ Hz, C=O), 167.77, 169.81, 173.73 (3C=O). ^{31}P NMR (121 MHz, CDCl$_3$): δ_P (ppm) 19.79 (P(C$_6$H$_5$)$_3$).

2.2. 1-Cyclohexyl-2,6-dioxo-5-(triphenyl-λ^5-phosphanylidene)-piperidine-3,4-dicarboxylic acid diethyl ester (4b)

Colorless crystals (0.36 g, yield 61%); mp 157–159 °C (dec). IR (KBr) (ν_{max}/cm^{-1}): 2925, 1729, 1673, 1592, 1433. MS, *m*/*z* (%): 599 (M$^+$, 2), 554 (2), 562 (100), 444 (7), 370 (15), 287 (7), 262 (20), 183 (30), 152 (7), 108 (13), 67 (17), 44 (47). ^{1}H NMR (300 MHz, CDCl$_3$): δ_H (ppm) 1.07 (3H, t, $^3J_{HH} = 7.1$ Hz, OCH$_2$C*H*$_3$), 1.25 (3H, t, $^3J_{HH} = 7.1$ Hz, OCH$_2$C*H*$_3$) 1.15–2.42 (10H, m, 5CH$_2$ of cyclohexyl), 3.00 (1H, dd, $^3J_{HP} = 11.9$ Hz, $^3J_{HH} = 2.0$ Hz, P=C–CH), 3.79 (1H, dd, $^4J_{HP} = 4.3$ Hz, $^3J_{HH} = 2.0$ Hz, P=C–CH–C*H*), 3.98–4.29 (4H, m, 2 OC*H*$_2$CH$_3$), 4.47 (1 H, tt, $^3J_{HH} = 11.8$ Hz, $^3J_{HH} = 3.3$ Hz, CH–N), 7.47–7.66 (15H, m, H–Ar of P(C$_6$H$_5$)$_3$). ^{13}C NMR (75 MHz, CDCl$_3$): δ_C (ppm) 13.98, 14.08 (2OCH$_2$*C*H$_3$), 25.44, 26.44, 26.59, 28.60, 29.83 (5CH$_2$ of cyclohexyl), 40.33 (d, $^2J_{PC} = 11.7$ Hz, P=C–*C*H), 42.62 (d, $^1J_{PC} = 135.7$ Hz, C=P), 52.23 (CH–N), 52.40 (d, $^3J_{PC} = 7.4$ Hz, P=C–CH–*C*H), 60.97, 61.77 (2 O*C*H$_2$CH$_3$), 125.52 (d, $^1J_{PC} = 92.9$ Hz, C_{ipso} of P(C$_6$H$_5$)$_3$), 128.71 (d, $^3J_{PC} = 12.4$ Hz, C_{meta} of P(C$_6$H$_5$)$_3$), 132.20 (d, $^3J_{PC} = 2.6$ Hz, C_{para} of P(C$_6$H$_5$)$_3$), 133.73 (d, $^2J_{PC} = 9.9$ Hz, C_{ortho} of P(C$_6$H$_5$)$_3$), 167.02 (d, $^2J_{PC} = 13.1$ Hz, C=O), 167.84, 169.45, 173.26 (3C=O). ^{31}P NMR (121 MHz, CDCl$_3$): δ_P (ppm) 20.19 (P(C$_6$H$_5$)$_3$).

2.3. 1-Cyclohexyl-2,6-dioxo-5-(triphenyl-λ^5-phosphanylidene)-piperidine-3,4-dicarboxylic acid di-*tert*-butyl ester (4c)

Colorless crystals (0.37 g, yield 56%); mp 200–201 °C (dec). IR (KBr) (ν_{max}/cm^{-1}): 2930, 1722, 1679, 1583, 1439. MS, *m*/*z* (%): 655 (M$^+$, 3), 554 (15), 454 (24), 372 (20), 262 (35), 183 (75), 152 (18), 108 (27), 77 (19), 57 (100), 41 (32).

2.3.1. Trans-isomer (63%). ^{1}H NMR (300 MHz, CDCl$_3$): δ_H (ppm) 1.09–2.40 (10H, m, 5CH$_2$ of cyclohexyl), 1.29, 1.41 (18H, 2s, 2OC(CH$_3$)$_3$), 2.98 (1H, dd, $^3J_{HP} = 11.9$ Hz, $^3J_{HH} = 2.0$ Hz, P=C–CH), 3.64–3.67 (1H, m, P=C–CH–C*H*), 4.49–4.55 (1H, m, CH–N), 7.45–7.70 (15H, m, H–Ar of P(C$_6$H$_5$)$_3$). ^{13}C NMR (75 MHz, CDCl$_3$): δ_C (ppm) 25.45, 26.62, 28.65, 29.98 (5CH$_2$ of cyclohexyl), 27.81, 27.97 (2OC(*C*H$_3$)$_3$), 40.88 (d, $^2J_{PC} = 11.5$ Hz, P=C–*C*H), 42.48 (d, $^1J_{PC} = 135.1$ Hz, C=P), 53.46 (CH–N), 54.35 (d, $^3J_{PC} = 8.0$ Hz, P=C–CH–*C*H), 81.18, 82.06 (2O*C*(CH$_3$)$_3$), 125.86 (d, $^1J_{PC} = 92.9$ Hz, C_{ipso} of P(C$_6$H$_5$)$_3$), 128.62 (d, $^3J_{PC} = 12.4$ Hz, C_{meta} of P(C$_6$H$_5$)$_3$), 132.06 (d, $^3J_{PC} = 2.9$ Hz, C_{para} of P(C$_6$H$_5$)$_3$), 133.93 (d, $^2J_{PC} = 10.0$ Hz, C_{ortho} of P(C$_6$H$_5$)$_3$), 167.05 (d, $^2J_{PC} = 13.2$ Hz, C=O), 168.14, 168.40, 172.64 (3C=O). ^{31}P NMR (121 MHz, CDCl$_3$): δ_P (ppm) 20.24 (P(C$_6$H$_5$)$_3$).

2.3.2. Cis-isomer (37%). ^{1}H NMR (300 MHz, CDCl$_3$): δ_H (ppm) 1.09–2.40 (10H, m, 5CH$_2$ of cyclohexyl), 1.38, 1.49 (18H, 2s, 2OC(CH$_3$)$_3$), 2.63 (1H, dd, $^3J_{HP} = 12.3$ Hz, $^3J_{HH} = 4.7$ Hz, P=C–C*H*), 3.64–3.67 (1H, m, P=C–CH–C*H*), 4.49–4.55 (1H, m, CH–N), 7.45–7.70 (15H, m, H–Ar of P(C$_6$H$_5$)$_3$). ^{13}C NMR (75 MHz, CDCl$_3$): δ_C (ppm) 25.32, 26.49, 28.93, 30.68 (5CH$_2$ of cyclohexyl), 27.92, 28.15 (2OC(*C*H$_3$)$_3$), 39.73 (d, $^2J_{PC} = 12.4$ Hz, P=C–*C*H), 44.32 (d, $^1J_{PC} = 133.6$ Hz, C=P), 52.35 (CH–N), 53.88 (d, $^3J_{PC} = 8.4$ Hz, P=C–CH–*C*H), 80.74, 81.51 (2O*C*(CH$_3$)$_3$), 125.68 (d, $^1J_{PC} = 92.9$ Hz, C_{ipso} of P(C$_6$H$_5$)$_3$), 128.76 (d, $^3J_{PC} = 12.3$ Hz, C_{meta} of P(C$_6$H$_5$)$_3$), 132.12 (d, $^3J_{PC} = 2.9$ Hz, C_{para} of P(C$_6$H$_5$)$_3$), 133.71 (d, $^2J_{PC} = 10.0$ Hz, C_{ortho} of P(C$_6$H$_5$)$_3$), 167.37 (d, $^2J_{PC} = 12.8$ Hz, C=O), 167.72 (d, $^2J_{PC} = 3.3$ Hz, C=O), 168.24, 172.24 (2C=O). ^{31}P NMR (121 MHz, CDCl$_3$): δ_P (ppm) 20.31 (P(C$_6$H$_5$)$_3$).

2.4. 1-*tert*-Butyl-2,6-dioxo-5-(triphenyl-λ^5-phosphanylidene)-piperidine-3,4-dicarboxylic acid diethyl ester (4d)

Colorless crystals (0.29 g, yield 51%); mp 151–153 °C (dec). IR (KBr) (ν_{max}/cm^{-1}): 2970, 1730, 1679, 1598, 1434. MS, *m*/*z* (%): 573 (M$^+$, 6), 500 (50), 444 (60), 370 (25), 287 (10), 278 (10), 262 (25), 201 (15), 183 (80), 152 (30), 108 (75), 77 (75), 57 (100). ^{1}H NMR (300 MHz, CDCl$_3$): δ_H (ppm) 1.16 (3H, t, $^3J_{HH} = 7.1$ Hz, OCH$_2$C*H*$_3$), 1.24 (3H, t, $^3J_{HH} = 7.1$ Hz, OCH$_2$C*H*$_3$) 1.54 (9H, s, OC(CH$_3$)$_3$), 3.05 (1H, dd, $^3J_{HP} = 13.3$ Hz, $^3J_{HH} = 2.3$ Hz, P=C–CH), 3.97 (1H, dd, $^4J_{HP} = 4.0$ Hz, $^3J_{HH} = 2.3$ Hz, P=C–CH–C*H*), 4.00–4.15 (4H, m, 2 OC*H*$_2$CH$_3$), 7.45–7.71 (15H, m, H–Ar of P(C$_6$H$_5$)$_3$). ^{13}C NMR (75 MHz, CDCl$_3$): δ_C (ppm) 13.84, 14.24 (2OCH$_2$*C*H$_3$), 29.49 (N–C(*C*H$_3$)$_3$), 40.75 (d, $^2J_{PC} = 11.5$ Hz, P=C–*C*H), 46.86 (d, $^1J_{PC} = 134.3$ Hz, C=P), 56.70 (d, $^3J_{PC} = 5.6$ Hz, P=C–CH–*C*H), 57.93 (d, $^4J_{PC} = 1.0$ Hz, N–*C*(CH$_3$)$_3$), 61.06, 61.65 (2O*C*H$_2$CH$_3$), 125.71 (d, $^1J_{PC} = 92.8$ Hz, C_{ipso} of P(C$_6$H$_5$)$_3$), 128.70 (d, $^3J_{PC} = 12.4$ Hz, C_{meta} of P(C$_6$H$_5$)$_3$), 132.26 (d, $^3J_{PC} = 2.8$ Hz, C_{para} of P(C$_6$H$_5$)$_3$), 133.84 (d, $^2J_{PC} = 10.0$ Hz, C_{ortho} of P(C$_6$H$_5$)$_3$), 168.46 (d, $^3J_{PC} = 1.4$ Hz, C=O), 168.94 (d, $^2J_{PC} = 14.0$ Hz, C=O), 169.80 (C=O), 173.54 (d, $^4J_{PC} = 2.1$ Hz, C=O). ^{31}P NMR (121 MHz, CDCl$_3$): δ_P 20.11 (ppm) (P(C$_6$H$_5$)$_3$).

Acknowledgements

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References and notes

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16. Crystal data analyses: Stoe IPDSII two-circle diffractometer, $Mo_{K\alpha}$ radiation ($\lambda = 1.71073$); $T = 293\,(2)$ K; Graphite monochromator; numerical absorption correction. Structure solution by direct methods using SHELXS and refinement by full-matrix least-squares on F^2 using SHELXL of the SHELXTL suite of programs;[21] all non-hydrogen atoms were refined anisotropically. Crystal data for **4b**: $C_{35}H_{38}NO_6P$, $M = 599.63\ g\,mol^{-1}$; crystal dimensions $0.10 \times 0.06 \times 0.01\ mm^3$; monoclinic, space group *Cc*; $a = 9.841\,(2)$, $b = 20.060\,(4)$, $c = 16.719\,(3)$ Å, $\beta = 100.38\,(3)°$, $V = 3246.5\,(11)$ Å^3; $Z = 4$; $F(000) = 1272$, $\rho_{calcd} = 1.23\ g\,cm^{-3}$; $2.03° < \theta < 26.50°$; section of the reciprocal lattice: $-11 \leqslant h \leqslant 15$, $-25 \leqslant k \leqslant 25$, $-20 \leqslant l \leqslant 20$; of 12,184 measured reflections, 12,184 were independent and 6140 with $I > 2\sigma(I)$; absorption coefficient $0.129\ mm^{-1}$; $R1 = 0.0626$ for $I > 2\sigma(I)$ and $wR2 = 0.0887$ (all data); largest peak ($0.196\ e\ Å^{-3}$) and hole ($-0.136\ e\ Å^{-3}$). (CCDC 295879).
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