Reaction of *C*-(Triphenylphosphinimido)hydrazones with Isocyanates as a Route to 5-Arylamino- and 5-Alkylamino-1*H*-1,2,4-triazoles

Luca Bruché, Luisa Garanti,* and Gaetano Zecchi
Dipartimento di Chimica Organica e Industriale dell'Università, Centro del C.N.R. per la Sintesi e Stereochimica di Speciali Sistemi Organici, 20133 Milano, Italy

Treatment of *C*-(triphenylphosphinimido)hydrazone (**1**) with aryl and alkyl isocyanates results in 5-arylamino- and 5-alkylamino-1*H*-1,2,4-triazoles (**5**), often accompanied by a minor quantity of the triazol-5-one (**7**). The related *ortho*-acyl-substituted substrates (**8**) react with phenyl isocyanate to give [1,2,4]triazolo[1,5-*a*]quinazolines (**12**) or (**13**) through the intermediacy of aminotriazoles (**11**).

We reported that compound (**1**) reacts with aldehydes to yield 1*H*-1,2,4-triazoles variously substituted in the 5 position.[1] In continuation of this line of research, we investigated the reaction of this peculiar kind of phosphinimide with isocyanates as a synthetic entry to 5-arylamino- and 5-alkylamino-1*H*-1,2,4-triazoles, a class of compounds of potential interest in pharmacology which are not readily accessible by other routes.[2,3]

Results and Discussion

Compound (**1**) was found to react with aryl isocyanates (**2a—g**) in benzene solution at room temperature in a time ranging from 3 to 120 h (see Scheme 1 and Table 1). In every case in addition to triphenylphosphine oxide, the reaction provided the aminotriazoles (**5**) in substantial yields along with a minor quantity of the triazolone (**7**). The relative proportion of the two ring-closed products was rather markedly dependent on the aryl substituent. The reaction of (**1**) with alkyl isocyanates (**2h,i**) required some heating to go to completion, and gave the aminotriazoles (**5**) in high yields with no formation of triazolone (**7**). In order to check whether the absence of the latter product was due to a substituent or a temperature effect, compound (**1**) was treated with butyl isocyanate (**2i**) at room temperature; after 8 days, only a part of the starting hydrazone had reacted, but the aminotriazole (**5i**) was shown to be again the exclusive product.

Since it is known that phosphinimides react with isocyanates to afford carbodi-imides,[4,5] the intermediates (**4**) represent the most plausible precursors of the final aminotriazoles (**5**). The formation of compound (**7**) is unexpected and may be due to a different breakdown of the phosphonium betaines (**3**), involving loss of triphenylphosphine phenylimide rather than oxide and giving the transient intermediate (**6**). The observed ratios (**5**):(**7**) vary greatly as a function of the R substituent, but their rationalisation is not simple. It seems that both electronic and steric factors influence the competition between the pathways (i) and (ii). With the idea of widening the synthetic utility of the reaction under study, we also prepared the related phosphinimides (**10a—c**) according to the sequence outlined in Scheme 2, and submitted them to reaction with phenyl isocyanate. The products were [1,2,4]triazolo[1,5-*a*]quinazolines (**12a**), (**12b**), and (**13**) from (**10a**), (**10b**), and (**10c**), respectively. The formation of these tricyclic compounds is well explained by further transformation of the aminotriazoles (**11**), which undergo an intramolecular cyclocondensation between the NH and CO groups.

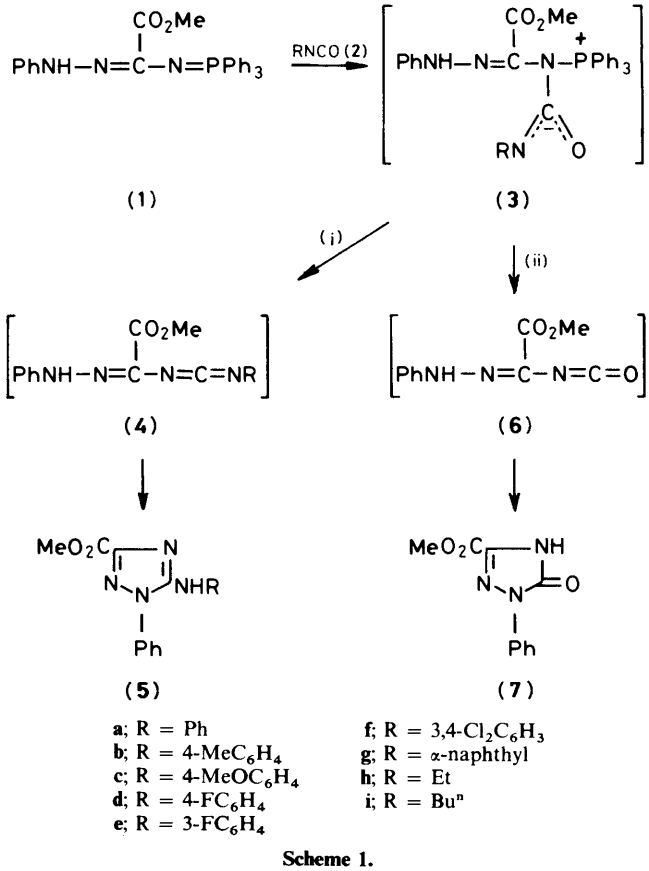
Experimental

M.p.s were determined with a Büchi apparatus and are uncorrected. I.r. spectra were recorded with a Perkin-Elmer 377 spectrophotometer. N.m.r. spectra were taken with Varian

Table 1. Reaction of *C*-(triphenylphosphinimido)hydrazones with isocyanates

Reactants	Temp.[a]	*t* (h)	Product(s)	Yield (%)
(**1**) + (**2a**)	r.t.	8	(**5a**) + (**7**)	67 + 21
(**1**) + (**2b**)	r.t.	30	(**5b**) + (**7**)	76 + 14
(**1**) + (**2c**)	r.t.	120	(**5c**) + (**7**)	69 + 15
(**1**) + (**2d**)	r.t.	3	(**5d**) + (**7**)	67 + 9
(**1**) + (**2e**)	r.t.	4	(**5e**) + (**7**)	47 + 20
(**1**) + (**2f**)	r.t.	96	(**5f**) + (**7**)	52 + 33
(**1**) + (**2g**)	r.t.	48	(**5g**) + (**7**)	52 + 27
(**1**) + (**2h**)	reflux	3	(**5h**)	75
(**1**) + (**2i**)	reflux	5	(**5i**)	70
(**10a**) + (**2a**)	reflux	4	(**12a**)	79
(**10b**) + (**2a**)	reflux	6	(**12b**)	80
(**10c**) + (**2a**)	reflux	6	(**13**)	73

[a] r.t. = room temperature.



Scheme 1.

Table 2. Preparation of *C*-azidohydrazones (**9a**—**c**) and *C*-(triphenylphosphinimido)hydrazones (**10a**—**c**)

Compd.	Yield (%)	M.p.[a] (°C)	$\nu_{max.}$/cm^{-1} (Nujol)	δ($CDCl_3$)	Elemental analysis (%) Found (required) C	H	N
(9a)	48	100—101	3 210, 2 120, 1 700, 1 670	1.40 (3 H, t), 4.40 (2 H, q), 7.0—7.7 (4 H, m), 9.96 (1 H, s), 11.6 (1 H, br s)	50.8 (50.6)	4.3 (4.2)	26.6 (26.8)
(9b)	50	139—140	3 240, 2 130, 1 710, 1 640	1.40 (3 H, t), 4.35 (2 H, q), 7.2—7.8 (8 H, m), 11.5 (1 H, br s)	54.6 (54.9)	3.8 (3.8)	18.9 (18.8)
(9c)	65	128—129	3 235, 2 120, 1 710, 1 650	1.45 (3 H, t), 2.70 (3 H, s), 4.40 (2 H, q), 6.9—7.9 (4 H, m), 12.0 (1 H, br s)	52.5 (52.4)	4.6 (4.8)	25.2 (25.4)
(10a)[b]	80	153—154[c]	3 250, 1 700, 1 650	1.10 (3 H, t), 4.00 (2 H, q), 6.8—7.9 (19 H, m), 9.98 (1 H, s), 12.0 (1 H, br s)	70.3 (70.3)	5.1 (5.3)	8.7 (8.5)
(10b)[d]	68	165—166[e]	3 250, 1 700, 1 640	1.10 (3 H, t), 4.00 (2 H, q), 6.9—8.1 (23 H, m), 12.2 (1 H, br s)	69.5 (69.4)	4.8 (4.8)	6.7 (6.9)
(10c)[f]	70	183—184[c]	3 240, 1 695, 1 645	1.10 (3 H, t), 2.65 (3 H, s), 4.00 (2 H, q), 6.6—8.1 (19 H, m), 12.5 (1 H, br s)	70.9 (70.7)	5.3 (5.5)	8.3 (8.2)

[a] From di-isopropyl ether–chloroform. [b] *m/z* 495 (M^+). [c] Yellow crystals. [d] *m/z* 605 (M^+). [e] Orange crystals. [f] *m/z* 509 (M^+).

Table 3. Physical, spectral, and analytical data of new heterocyclic compounds[a]

Compd.	M.p.[b] (°C)	$\nu_{max.}$/cm^{-1} (Nujol)	δ($CDCl_3$)	Elemental analysis (%) Found (required) C	H	N
(5a)	158	3 345, 1 720	4.01 (3 H, s), 6.6 (1 H, br s), 7.0—7.7 (10 H, m)	65.4 (65.3)	4.9 (4.8)	18.8 (19.0)
(5b)	123	3 345, 1 720	2.33 (3 H, s), 4.03 (3 H, s), 6.5 (1 H, br s), 7.0—7.7 (9 H, m)	66.4 (66.2)	5.2 (5.2)	18.3 (18.2)
(5c)	137	3 340, 1 720	3.80 (3 H, s), 4.00 (3 H, s), 6.6—6.8 (2 H, m), 6.9 (1 H, br s), 7.3—7.6 (7 H, m)	62.9 (62.9)	4.8 (5.0)	17.4 (17.3)
(5d)	141	3 320, 1 715	4.01 (3 H, s), 6.6 (1 H, br s), 6.9—7.7 (9 H, m)	61.5 (61.5)	4.0 (4.2)	17.8 (17.9)
(5e)	196	3 340, 1 720	4.01 (3 H, s), 6.5—7.7 (9 H, m), 8.2 (1 H, br s)	61.7 (61.5)	4.2 (4.2)	18.0 (17.9)
(5f)	191	3 320, 1 710	4.00 (3 H, s), 7.0—7.9 (8 H, m), 8.4 (1 H, br s)	53.0 (52.9)	3.1 (3.3)	15.4 (15.4)
(5g)	171	3 320, 1 720	3.95 (3 H, s), 6.9 (1 H, br s), 7.2—8.1 (12 H, m)	69.9 (69.7)	4.8 (4.7)	16.4 (16.3)
(5h)	*c*	3 330, 1 730	1.18 (3 H, t), 3.2—3.6 (2 H, m),[d] 3.90 (3 H, s), 4.62 (1 H, t, *J* 6 Hz, exchangeable), 7.3—7.6 (5 H, m)	58.6 (58.5)	5.8 (5.7)	22.7 (22.7)
(5i)	*e*	3 320, 1 725	1.1—1.7 (7 H, m), 3.2—3.6 (2 H, m),[d] 3.89 (3 H, s), 4.70 (1 H, t, *J* 6 Hz, exchangeable), 7.40 (5 H, m)			
(7)	198	1 740, 1 715	4.08 (3 H, s), 7.1—7.6 (4 H, m), 7.9—8.2 (2 H, m)	54.8 (54.8)	4.2 (4.1)	19.1 (19.2)
(12a)	171	3 320, 1 715	1.40 (3 H, t), 4.34 (2 H, q), 5.15 (1 H, d, *J* 7 Hz, exchangeable), 6.22 (1 H, d, *J* 7 Hz),[f] 7.2—7.9 (9 H, m)	64.5 (64.3)	4.7 (4.8)	16.6 (16.7)
(12b)	182	3 320, 1 740	1.34 (3 H, t), 1.6 (1 H, br s), 4.35 (2 H, q), 6.8—8.0 (13 H, m)	64.6 (64.5)	4.3 (4.3)	12.7 (12.5)
(13)[g]	128	1 720	1.42 (3 H, t), 4.47 (2 H, q), 3.92 (1 H, d, *J* 3 Hz), 4.84 (1 H, d, *J* 3 Hz), 7.1—8.0 (9 H, m)	68.6 (68.7)	4.9 (4.8)	16.9 (16.9)

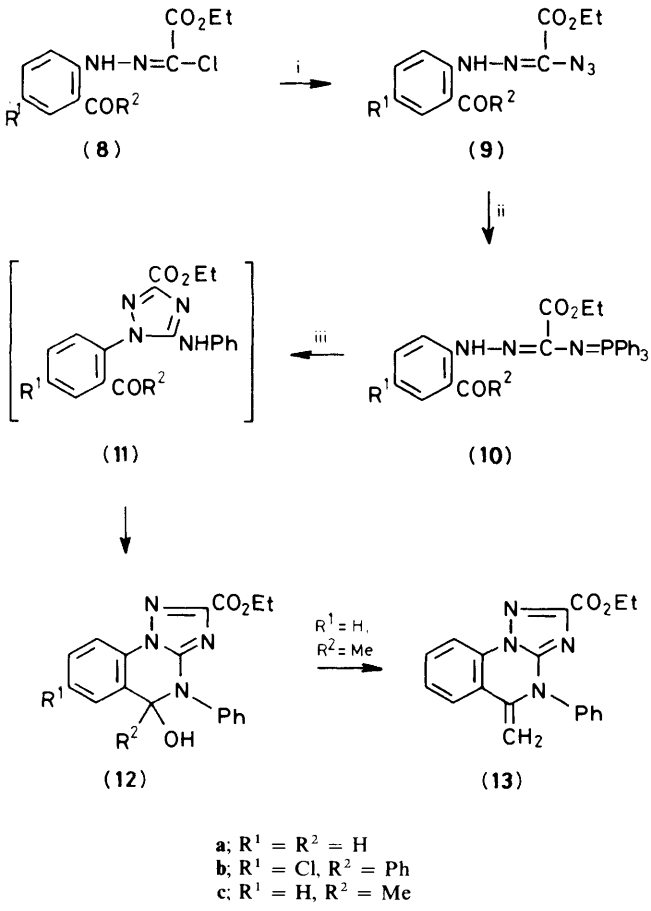
[a] Correct molecular peaks were observed in the mass spectra. [b] From di-isopropyl ether–chloroform. [c] B.p. 240—245 °C/0.1 mmHg. [d] Triplet after deuteriation of the NH group. [e] Undistilled oil. [f] Singlet after deuteriation of the OH group. [g] δ_C($CDCl_3$) 14.2 (q), 62.0 (t), 88.0 (t), 115.7 (d), 120.1—131.5 (set of signals), 137.5 (s), 141.5 (s), 151.0 (s), and 159.9 (s).

EM-390 (^{1}H) and Bruker WP80SY (^{13}C) instruments; chemical shifts are given in p.p.m. from internal $SiMe_4$. Compounds (**1**),[1] (**8a**),[6] and (**8b**)[7] are known in the literature. Compound (**8c**) was prepared (79% yield; m.p. 123 °C) from 2-acetylaniline according to the procedure described for compound (**8a**).[6] Light petroleum refers to the fraction boiling in the range 40—60 °C.

Reaction of Hydrazone (**1**) *with Aryl Isocyanates* (**2a**—**g**).—A solution of compound (**1**) (3 mmol) and an isocyanate (**2**) (3 mmol) in dry benzene (150 ml) was left at room temperature for the time given in Table 1. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column with light petroleum—ethyl acetate (1:1) as eluant. Products and yields are given in Tables 1 and 3.

Reaction of Hydrazone (**1**) *with Alkyl Isocyanates* (**2,i**).—A solution of compound (**1**) (3 mmol) and an isocyanate (**2h** or **i**) (15 mmol) in dry benzene (150 ml) was refluxed for the time given in Table 1. The solvent was evaporated off under reduced pressure and the residue was chromatographed on a silica gel column with light petroleum–ethyl acetate (1:1) as eluant. The products and yields are shown in Tables 1 and 3.

Preparation of Azidohydrazones (**9a**—**c**).—A solution of a chlorohydrazone (**8**) (10 mmol) in benzene (100 ml) was treated



a; $R^1 = R^2 = H$
b; $R^1 = Cl$, $R^2 = Ph$
c; $R^1 = H$, $R^2 = Me$

Scheme 2. *Reagents*: i, NaN_3; ii, PPh_3; iii, PhNCO

with an aqueous solution (100 ml) of sodium azide (0.1 mol) and hexadecyltributylphosphonium bromide (1 mmol). The vigorously stirred mixture was heated at 50 °C for 6 h in the dark. The organic layer was separated, washed with water, dried over Na_4SO_4, and evaporated under reduced pressure. The residue was chromatographed on a silica gel column with dichloromethane as eluant. Product yields and data are in Table 2.

Preparation of (Triphenylphosphinimido)hydrazones (**10a**—**c**).—A solution of an azide (**9**) (6 mmol) and triphenylphosphine (6 mmol) in dry diethyl ether (200 ml) was refluxed for 2 h. After evaporation of the solvent, the crude product was purified by chromatography on a silica gel column with dichloromethane as eluant. See Table 2 for product yields and data.

Reaction of Hydrazones (**10a**—**c**) *with Phenyl Isocyanate.*—A solution of a phosphinimide (**10**) (1 mmol) and compound (**2a**) (1 mmol) in dry benzene (50 ml) was refluxed for the time indicated in Table 1. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column with light petroleum–ethyl acetate (1:1) as eluant. For yields and data for products (**12**) and (**13**) see Tables 1 and 3.

References

1 L. Bruché, L. Garanti, and G. Zecchi, *Synthesis*, 1985, 304.
2 J. H. Boyer, in 'Heterocyclic Compounds,' ed. R. C. Elderfield, Wiley, London, 1961, vol. 7, ch. 5.
3 C. Temple, Jr., 'Triazoles-1,2,4,' ed. J. A. Montgomery, Interscience, New York, 1981, pp. 144 and 297.
4 E. Fluck, *Top. Phosphorus Chem.*, 1967, 414.
5 J. I. G. Cadogan and R. K. Mackie, *Chem. Soc. Rev.*, 1974, **3**, 87.
6 V. Evdokimoff, *Gazz. Chim. Ital.*, 1957, **87**, 1191.
7 V. Evdokimoff, *Boll. Chim. Farm.*, 1970, **109**, 240 (*Chem. Abstr.*, 1970, **73**, 77155).

Received 15*th January* 1986; *Paper* 6/117