1,2,4-Triazole-Fused Heterocycles; Part 1: Preparation of 5,10-Dihydro-[1,2,4]-triazolo[5,1-*b*]quinazolines

Kee-Jung Lee,*[a] Seong Heon Kim,[b] Sanghee Kim,[b] Hokoon Park,[b] Yang Rai Cho,[c] Bong Young Chung,[c] Edward E. Schweizer[d]

[a] Department of Industrial Chemistry. Hanyang University, Seoul 133-791, South Korea
[b] Division of Chemistry, Korea Institute of Science and Technology, P.O. Box 131, Seoul 130-650, South Korea
[c] Department of Chemistry, Korea University, Seoul 136-701, South Korea
[d] Department of Chemistry and Biochemistry, University of Delaware, Newark, Delaware 19716, USA

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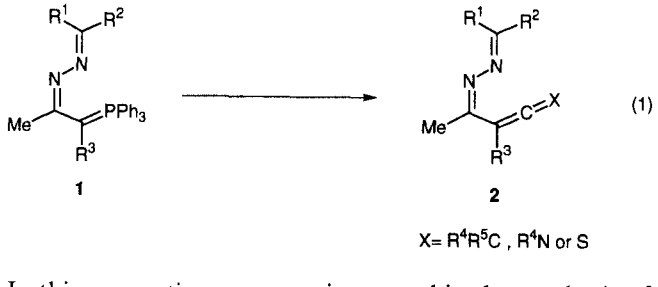
The reaction of benzophenone 1-ureidoethylidenehydrazones **9** with a mixture of triphenylphosphine, carbon tetrachloride, and triethylamine in dichloromethane provides a general route to 5,10-dihydro-[1,2,4]triazolo[5,1-*b*]quinazolines **7** via the electrocyclization of the expected azino carbodiimide intermediates **10**. When one of the substituents on the ureas **9** was an aryl group, unusual guanidine compounds **13** were also produced, and their structures were confirmed by X-ray crystallographic analysis.

In recent years, there has been a significant interest in the chemistry of iminophosphoranes because of their utility in the synthesis of a wide variety of nitrogen heterocycles, and many interesting heterocyclization reactions involving functionalized iminophosphoranes have been reviewed.[1] Also, the reactions of azine ylides **1** with isocyanates, ketenes, and other species that contain carbonyl or thiocarbonyl moieties have provided excellent syntheses of a variety of pyrazolo-fused heterocyclic compounds via conjugated heterocumulenes **2** (Eq 1).[2]



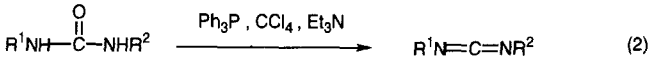
1 **2** (1)

X= R^4R^5C , R^4N or S

In this connection, we were interested in the synthesis of their nitrogen homologues, 1,2,4-triazolo-fused heterocyclic systems, and we expected on the basis of previous work[3] that the reaction of iminophosphorane **5** with isocyanates would give the novel [1,2,4]triazolo[5,1-*b*]quinazolines **7** or **8** via carbodiimide intermediates **6**. A number of reports in the literature[4] have shown that on reacting iminophosphoranes with isocyanates carbodiimide products occur readily.

The key iminophosphorane **5** was easily prepared by the reaction of a mixture of triphenylphosphine and iodine[5] with benzophenone 1-aminoethylidenehydrazone **(4)**, which was readily obtainable by the reaction of *S*-methyl thioacetimidate hydroiodide[6] **(3)** with benzophenone hydrazone followed by neutralization with aqueous sodium hydrogen carbonate. The ^{31}P NMR spectrum of the compound **5** shows a signal at $\delta = 31.84$ [$CDCl_3$/$(PhO)_3PO$] due to the highly conjugated iminophosphorane moiety. However, aza-Wittig reaction of **5** with an equimolecular amount of phenyl isocyanate in dichloromethane at reflux temperature led directly to only a poor yield of the expected 5,10-diphenyl-5,10-dihydro-[1,2,4]triazolo[5,1-*b*]quinazoline (**7a**, 19%),[7] presumably via the carbodiimide intermediate **6** (Scheme 1).

On the other hand, it is well known that carbodiimides are readily obtained from *N,N'*-disubstituted ureas with triphenylphosphine, carbon tetrachloride, and triethylamine in dichloromethane according to the method developed by Appel and co-workers (Eq 2).[8] We now wish to report a simple method for the synthesis of [1,2,4]triazolo[5,1-*b*]quinazolines **7** from the azino ureas **9** based on the dehydration and subsequent electrocyclic ring closure of the azino carbodiimide intermediate **10**, and the unexpected guanidine compounds **13**.



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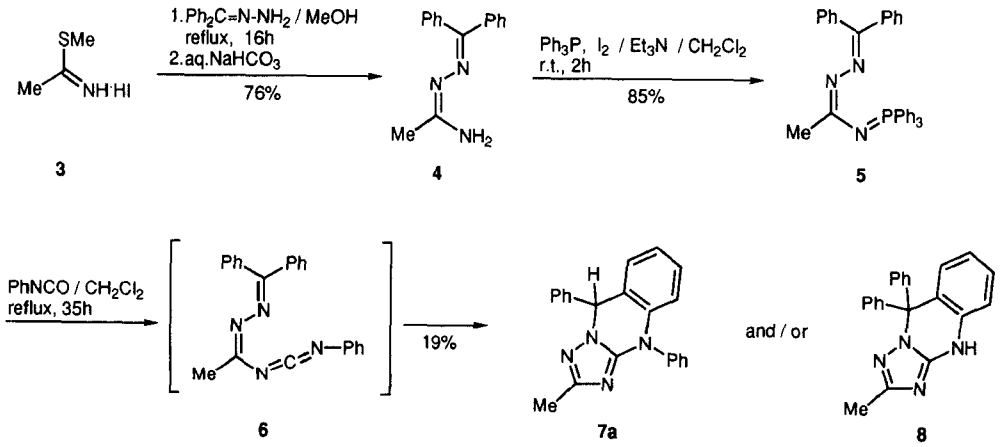
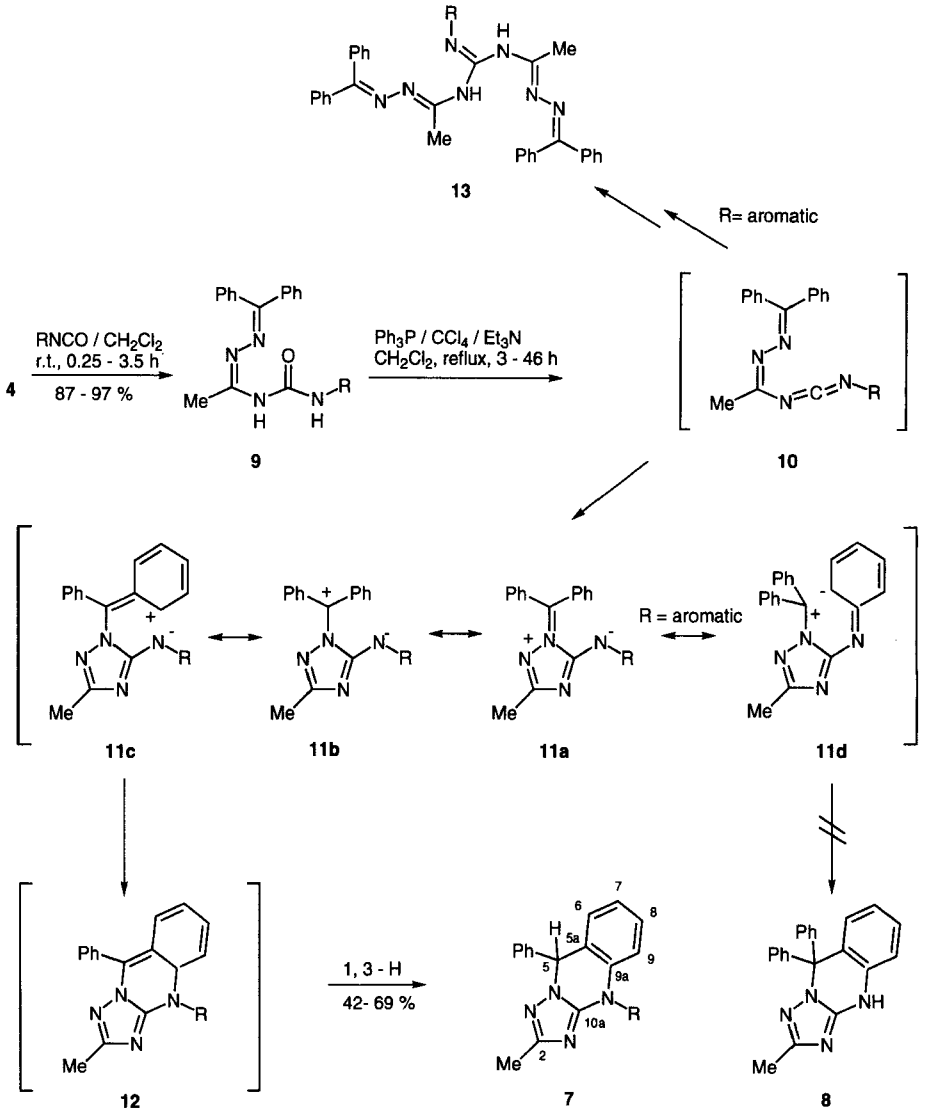


Scheme 1

The starting compounds, benzophenone 1-ureidoethylidenehydrazones **9**, were obtained by the reaction of benzophenone 1-aminoethylidenehydrazone **(4)** with isocyanates in dichloromethane (Table 1). Treatment of **9** with triphenylphosphine, carbon tetrachloride, and triethylamine in dichloromethane at reflux temperature smoothly afforded the desired [1,2,4]triazolo[5,1-*b*]quinazolines **7** in yields of 42–69% (Table 2). Interestingly, 5,5-diphenyl-5,10-dihydro-[1,2,4]triazolo[5,1-*b*]quinazolines **8** were not produced, but unusual guanidines **13a–f** were obtained in the reaction of aryl ureas **9a–f**.

A reasonable mechanism for the transformation of **9** into **7** is shown in Scheme 2. Although the isolation of carbodiimide azine **10** was unsuccessful under the reaction conditions,[9] we recognize that the mechanistic sequence depicted (**10** → **11** → **12** → **7**) may involve an electrocyclization of the carbodiimide azine **10** to give the resonance stabilized azomethine imine **11** followed by ring closure to form **12** and the 1,3-hydride shift to give **7**.

Structural elucidation of **7** was accomplished on the basis of spectral data and microanalyses. The ^{1}H NMR spectra



7, 9, 13	R	7, 9	R
a	C_6H_5	g	Me
b	4-ClC_6H_4	h	n-Bu
c	4-$O_2NC_6H_4$	i	4-$MeC_6H_4SO_2$
d	4-$CF_3C_6H_4$		
e	4-MeC_6H_4		
f	4-$MeOC_6H_4$		

Scheme 2

Table 1. Benzophenone 1-Ureidoethylidenehydrazones **9** Prepared

Compound[a]	Reaction Time (h)	Yield[b] (%)	mp (°C)	^{1}H NMR (DMSO-d_6/TMS) δ, J (Hz)			
				CH_3[c]	Aromatic	Two NH[d]	Others
9a	0.25	97	195–197	2.40	6.57–7.80 (m, 15H)	9.60, 11.17	
9b	1	97	193–194	2.37	6.56–7.54 (m, 14H)	9.73, 11.21	
9c	0.5	94	220–222	2.39	6.70–8.02 (m, 14H)	9.99, 11.72	
9d	0.33	97	208–209 (dec)	2.38	6.71–7.66 (m, 14H)	9.85, 11.46	
9e	0.5	97	202–203	2.20	6.47–7.54 (m, 14H)	9.63, 10.99	2.37 (s, 3H, CH_3)
9f	0.5	94	208–210	2.36	6.52–7.55 (m, 14H)	9.60, 10.90	3.70 (s, 3H, OCH_3)
9g	1	95	200–202 (dec)	2.26	7.21–7.60 (m, 10H)	8.51 (q, J = 4.5, 1H), 9.24 (s, 1H)	2.24 (d, J = 4.5, 3H, $NHCH_3$)
9h	3.5[e]	87	129–130	2.28	6.90–7.90 (m, 10H)	8.55, 9.10	0.65–1.70 (m, 7H), 2.50–2.93 (m, 2H)
9i	0.25	90	156–158	2.38	7.15–7.85 (m, 14H)	10.71, 11.82	2.40 (s, 3H, CH_3)

[a] Satisfactory microanalyses were obtained: C ± 0.28, H ± 0.19, N ± 0.26.
[b] Yield of pure isolated product.
[c] All singlets.
[d] All broad singlets, except for **9g**.
[e] Reflux temperature.

showed a characteristic peak at δ = 2.23–2.39 for the C2-methyl protons, and the C5-proton resonated in the δ = 6.05 to 6.61 region. The aromatic multiplets ranged from δ = 6.54 to 8.48. The characteristic signals found in the ^{13}C NMR spectra appear as follows: δ = 14.4–14.7 (C2–$\underline{C}H_3$), 159.1–160.5 (C2), 146.5–151.3 (C10a), 135.0–138.0 (C9a), 113.0–115.3 (C9), 121.8–123.7 (C6), 120.5–121.5 (C5a), and C5-carbons ranged from δ = 62.0 to 62.4. These ^{1}H and ^{13}C NMR values are in good agreement with those reported for a similar system.[10] Interestingly, the absorption of C5-carbons in the ^{13}C NMR spectra were shown as two peaks except with **7b**, **7d**, and **7i**.

The yellow secondary products **13**, isolated in 2–28% yield, were also established on the basis of spectral data and microanalyses. On examining the ^{1}H NMR of **13a**, we identified two methyl peaks at δ = 1.54 and 2.51, and two NH peaks at δ = 11.36 and 12.91, and 25 aromatic hydrogens. As we were unable to determine conclusively the structure, an X-ray analysis of a single crystal was performed; an ORTEP diagram is shown in Figure 1. Why the aryl ureas **9a–f** only produce the guanidine derivatives **13a–f**, and the mechanistic pathway of the formation of **13** are uncertain.[11]

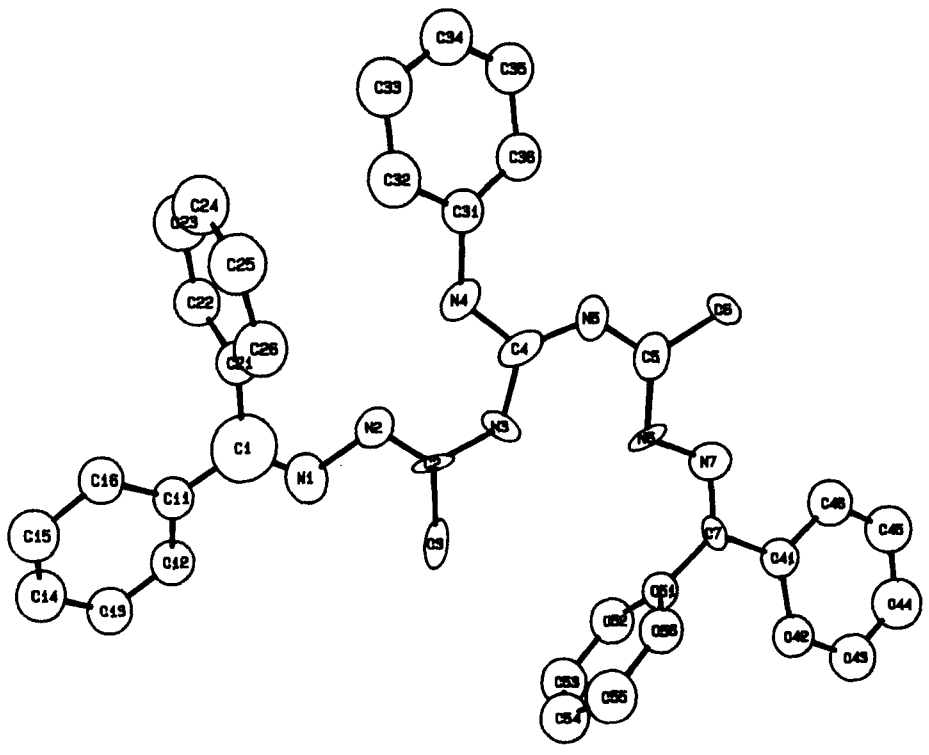


Figure 1

Table 2. 5,10-Dihydro-[1,2,4]triazolo[5,1-*b*]quinazolines **7** Prepared

Compound[a]	Reaction Time (h)	Yield[b] (%)	mp (°C) (solvent)	^{1}H NMR ($CDCl_3$/TMS) δ, J (Hz)				Selected ^{13}C NMR[d] ($CDCl_3$) δ								
				C2-CH_3[c]	C5-H[c]	Aromatic	Others	C2	C2-CH_3	C10a	C9a	C9	C6	C5a	C5	Others
7a	46	69	167–168 (CH_2Cl_2)	2.26	6.61	6.65–7.65 (m, 14 H)		159.6	14.7	150.9	137.8	115.1	122.6	120.7	62.39, 62.31	
7b	36	52	223–224 (EtOH)	2.23	6.57	6.54–7.60 (m, 13 H)		159.5	14.6	150.6	137.3	115.0	122.9	120.8	62.32	
7c	7	55	239–240 (EtOH)	2.24	6.58	6.67–8.48 (m, 13 H)		159.5	14.5	149.9	136.5	115.3	123.7	121.5	62.28, 62.20	
7d	12	52	242–243 (EtOH)	2.25	6.59	6.56–7.89 (m, 13 H)		159.5	14.5	150.3	137.0	115.0	123.1	121.0	62.27	
7e	31	62	213–214 (EtOH)	2.23	6.57	6.56–7.42 (m, 13 H)	2.46 (s, 3 H, CH_3)	159.6	14.7	151.0	137.8	115.1	122.4	120.5	62.37, 62.29	21.4 (CH_3)
7f	7	42	215–216 (EtOAc)	2.23	6.57	6.54–7.40 (m, 13 H)	3.89 (s, 3 H, OCH_3)	159.6	14.7	151.2	138.0	115.0	122.5	120.5	62.35, 62.28	55.4 (OCH_3)
7g	44	61	119–121	2.30	6.48	7.00–7.35 (m, 9 H)	3.63 (s, 3 H, NCH_3)	159.1	14.4	151.3	136.7	112.7	122.1	120.9	62.17, 62.10	32.1 (NCH_2)
7h	6	65	103–105 (Hexane)	2.29	6.46	6.94–7.35 (m, 9 H)	1.01 (t, J = 7.3, 3 H, CH_3), 1.52 (m, 2 H, CH_2), 1.80 (m, 2 H, CH_2), 4.13 (m, 2 H, NCH_2)	159.2	14.6	151.0	135.6	113.0	121.8	121.0	62.19, 62.14	44.7 (NCH_2), 29.0 (CH_2), 20.1 (CH_2), 13.7 (CH_3)
7i	3	51	75–77 (Et_2O/ Hexane)	2.39	6.05	6.89–7.93 (m, 13 H)	2.42 (s, 3 H, CH_3)	160.5	14.7	146.5	135.0	–[e]	–[e]	–[e]	62.00	21.7 (CH_2)

[a] Satisfactory microanalyses were obtained: C ± 0.28, H ± 0.18, N ± 0.26.
[b] Yield of pure isolated product.
[c] All singlets.
[d] Unable to assign C7 and C8 of many aromatics. Numbering of **7** shown in Scheme 2.
[e] Unable to assign.

Table 3. Guanidine Compounds **13** Prepared

Compound[a]	Yield[b] (%)	mp (°C) (Et_2O)	^1H NMR ($CDCl_3$/TMS) δ			
			two CH_3[c]	Aromatic	Two NH[c]	Others[c]
13a	15	196–197	1.54, 2.51	6.88–7.69	11.36, 12.91	
13b	27	182–183	1.51, 2.46	6.76–7.65	11.44, 12.87	
13c	9	216–217	1.53, 2.50	6.90–7.96	11.94, 12.86	
13d	28	185–186	1.56, 2.52	6.94–7.70	11.66, 12.89	
13e	2	176–177[d]	1.49, 2.45	6.72–7.65	11.22, 12.87	2.27 (CH_3)
13f	4	170–171[d]	1.51, 2.45	6.64–7.66	11.20, 12.85	3.79 (OCH_3)

[a] Satisfactory microanalyses were obtained: C ± 0.24, H ± 0.19, N ± 0.30.
[b] Yield of pure isolated product.
[c] All singlets.
[d] Recrystallized from Et_2O/petroleum ether.

We have thus worked out a useful and simple method for the synthesis of [1,2,4]triazolo[5,1-*b*]quinazolines **7** and guanidine derivatives **13** from azino ureas **9**. Further studies into the preparation of other triazole-fused heterocycles from cumulated azine synthons are underway.

CCl_4 and CH_2Cl_2 were dried and distilled from P_2O_5. Et_3N was dried and distilled from sodium metal. Silica gel EM 7747 for column chromatography was used throughout for product separation. Melting points were taken using an Electrothermal melting point apparatus and are uncorrected. Microanalyses were obtained using a Perkin-Elmer 240 DS element analyzer. Compounds **4** and **5** gave C, H, N analysis ± 0.29% (for other compounds, see Tables). Mass spectra were obtained using a Hewlett Packard model 5985 B spectrometer. ^1H and ^{13}C NMR spectra were measured on a Varian Gemini 300 spectrometer, and ^{31}P NMR spectra were measured on a Bruker AM-200 spectrometer. X-ray structure determination was confirmed using an Enraf-Nonius CAD4 automatic diffractometer.

The *S*-methyl thioacetimidate hydroiodide (**3**) was prepared following the literature procedure.[6] Benzophenone hydrazone and isocyanates were purchased from Aldrich Chemical Co.

Benzophenone 1-Aminoethylidenehydrazone (4):
To a solution of *S*-methyl thioacetimidate hydroiodide (**3**) (43.4 g, 0.20 mol) in MeOH (150 mL) was added benzophenone hydrazone (41.2 g, 0.21 mol) and this solution was stirred at reflux temperature for 16 h. After cooling, the solution was concentrated to dryness, and the residual material was dissolved in CH_2Cl_2 (300 mL) and washed with 10% aq $NaHCO_3$ (200 mL). The organic layer was separated, dried ($MgSO_4$), concentrated to dryness, and crystallized from Et_2O to give the product **4**; yield 36.1 g (76%); mp 103–104°C.
^1H NMR ($CDCl_3$/TMS): δ = 1.91 (s, 3H, CH_3), 4.93 (br s, 2H, NH_2), 7.25–7.58 (m, 10 H_{arom}).

Benzophenone 1-[(Triphenylphosphoranylidene)amino]ethylidenehydrazone (5):
To a solution of Ph_3P (866 mg, 3.3 mmol) in CH_2Cl_2 (30 mL) was added I_2 (761 mg, 3.0 mmol) at r.t. The resulting reaction mixture was stirred at r.t. for 0.5 h and then treated with Et_3N (0.92 mL, 6.6 mmol) followed immediately by the addition of aminoethylidenehydrazone **4** (712 mg, 3.0 mmol). After stirring for 2 h at r.t., the reaction mixture was poured into H_2O (20 mL) and extracted with CH_2Cl_2 (2 × 20 mL). The combined extracts were dried ($MgSO_4$), concentrated to dryness, and crystallized from EtOAc–hexane to give the product **5**; yield 1.27 g (85%); mp 171–172°C.
^1H NMR ($CDCl_3$/TMS): δ = 2.61 (d, J = 2.7 Hz, 3H, CH_3), 6.78–7.67 (m, 25 H_{arom}).
^{31}P NMR [$CDCl_3$/$(PhO)_3PO$]: δ = 31.84.

5,10-Diphenyl-5,10-dihydro-[1,2,4]triazolo[5,1-*b*]quinazoline (7a):
To a solution of iminophosphorane **5** (498 mg, 1.0 mmol) in CH_2Cl_2 (10 mL) was added PhNCO (0.12 mL, 1.05 mmol) at r.t. The mixture was stirred at reflux temperature for 35 h whereupon the solvent was removed under reduced pressure. The residual material was chromatographed (silica gel; EtOAc–hexane, 1:3) to give **7a**; yield 64 mg (19%); mp 167–168°C (CH_2Cl_2).
MS (EI, 70 eV): m/z = 338 (M^+, 23%), 262 (17), 261 (100).
^1H NMR ($CDCl_3$/TMS): δ = 2.26 (s, 3H, CH_3), 6.61 (s, 1H, C5-H), 6.65–7.65 (m, 14 H_{arom}).

Benzophenone 1-Ureidoethylidenehydrazones 9; General Procedure:
To a stirred solution of benzophenone 1-aminoethylidenehydrazone (**4**) (1.18 g, 5.0 mmol) in CH_2Cl_2 (20 mL) was added RNCO (5.5 mmol) at r.t. After stirring for the time indicated in Table 1 at r.t., the reaction mixture was concentrated and the resulting solid was triturated with Et_2O, separated by filtration, and dried in vacuo to give **9** as pale yellow solid (Table 1).

5,10-Dihydro-[1,2,4]triazolo[5,1-*b*]quinazolines 7 and *N,N'*-Bis-(4,4-diphenyl-1-methyl-2,3-diazabuta-1,3-dien-1-yl)-*N''*-phenylguanidines 13; General Procedure:
To a stirred suspension of the appropriate urea **9** (2.0 mmol) in CH_2Cl_2 (20 mL) was added Ph_3P (787 mg, 3.0 mmol), CCl_4 (0.77 mL, 8.0 mmol), and Et_3N (0.42 mL, 3.0 mmol) at r.t. The mixture was heated at reflux temperature for the time indicated in Table 2, and the resulting solution was concentrated to dryness. The residual material was chromatographed (silica gel; EtOAc–hexane, 1:3) to give **7** as a white or pale yellow solid (Table 2).

In the case of aryl ureas **9a–f**, a yellow crystalline product **13a–f** was eluted first during chromatography (Table 3).

Crystallographic Structure Determination of 13a:
All the crystallographic data were obtained at 21°C with an Enraf-Nonius CAD 4 automatic diffractometer. All software is contained in the SHELX-76 software package. For **13a**, $C_{37}H_{33}N_7$, orthorhombic, $P2_12_12_1$ a = 7.221(2), b = 15.345(5), c = 28.233(5) Å, V = 3128 Å^3, z = 4, D (calc.) = 1.222 gcm^{-3}, μ = 0.41 cm^{-1}. Of 1440 reflections collected ($3° \leq 2\theta \leq 50°$), 1104 unique reflections with $I > 3\sigma(I)$ were considered observed. No absorption correction was applied. Solution was by direct methods and difference Fourier synthesis. Anisotropic refinement of all non-hydrogen atoms except carbon atoms of phenyl rings and an idealized treatment of hydrogen-atom contributions led to these final parameters: R = 8.11%, R_w = 8.40%, GOF = 1.19, $\Delta\varrho$ (max) = 0.4. Tables of atomic coordinates, bond distances and angles, and anisotropic temperature coefficents are available as supplementary material from the authors.

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