PREPARATION OF 3,4-DIARYL-4,5-DIHYDRO-1*H*-1,2,4-TRIAZOLE-1-*N*-PHENYLCARBOXAMIDES†

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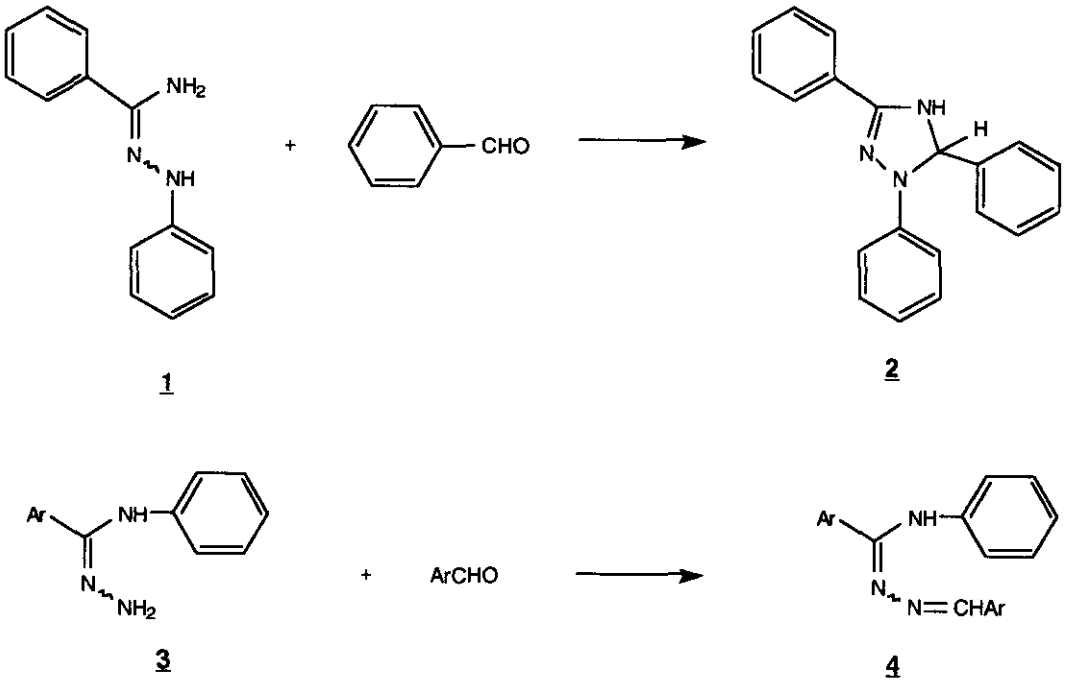
Abstract - N^3-Arylbenzamidrazone (**5**) reacts with aldehydes and ketones to give the corresponding hydrazones (**6**) rather than the tautomeric 4,5-dihydro-1*H*-1,2,4-triazoles (**7**). Treatment of the hydrazones (**6**) with α,α,α-trifluoro-*p*-tolyl isocyanate gives 3,4-diaryl-4,5-dihydro-1*H*-1,2,4-triazole-1-carboxamides (**8**). This suggests that, in solution, hydrazones (**6**) exist in equilibrium with low levels of the more nucleophilic 4,5-dihydro-1*H*-1,2,4-triazoles (**7**) which are trapped by isocyanate to give triazolines of formula (**8**).

It is known that certain 4,5-dihydro-1*H*-1,2,4-triazoles can be prepared by the condensation of amidrazones with aldehydes and ketones.[2] However, this method is limited by the fact that the product obtained is often the open-chain hydrazone rather than the tautomeric 4,5-dihydro-1*H*-1,2,4-triazole. For example, N^1-phenylbenzamidrazone (**1**) condenses with benzaldehyde to give 4,5-dihydro-1,3,5-triphenyl-1*H*-1,2,4-triazole (**2**)[3] while N^3-phenylamidrazones (**3**) condense with aldehydes to give hydrazones (**4**) rather than the tautomeric 4,5-dihydro-3,4,5-triaryl-1*H*-1,2,4-triazoles[4] (Scheme 1).

As part of a program to identify new classes of insecticides, we sought to prepare a series of 3,4-*diaryl-4,5-dihydro-1H-1,2,4-triazole-1-carboxamides of general formula* (***8***) *(Scheme 2)*. Although the above-mentioned finding of Spassov *et al.*[4] suggests that N^3-phenylamidrazones (**3**) are not

Scheme 1

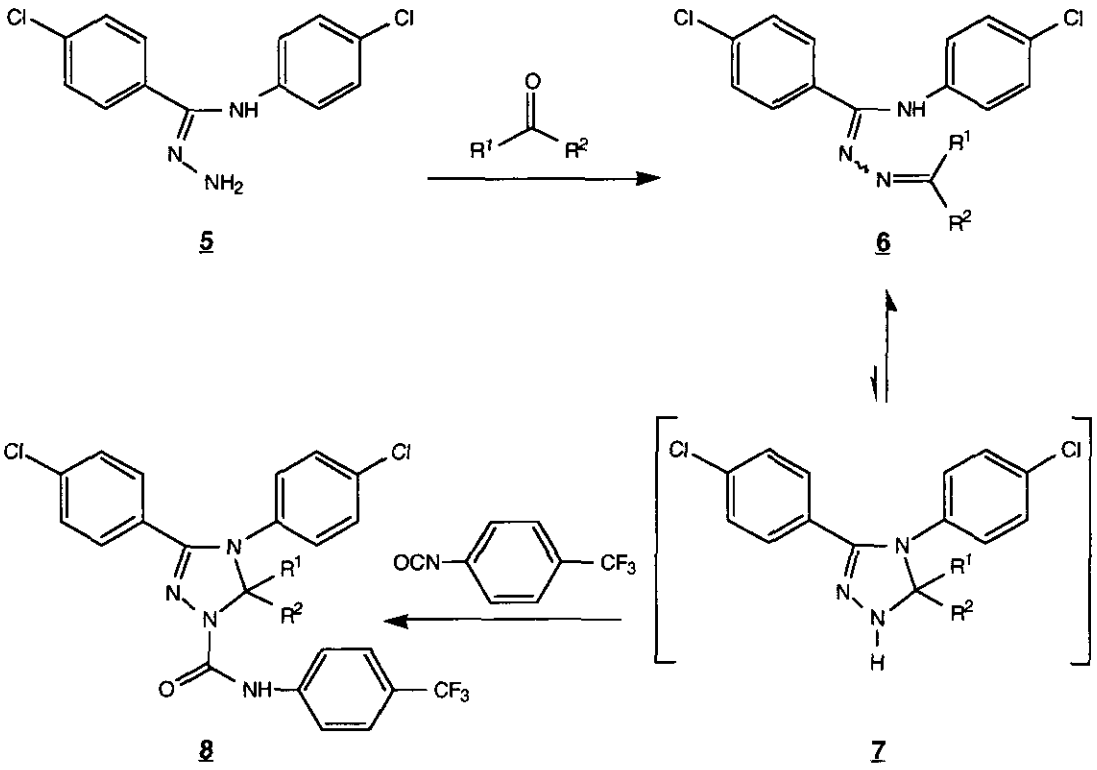


useful precursors to 4,5-dihydro-3,4,5-triaryl-1*H*-1,2,4-triazoles, the simplicity and potential versatility of the amidrazone route to 4,5-dihydro-1*H*-1,2,4-triazoles led us to explore the use of amidrazone hydrazones as precursors to compounds of formula (**8**). We were encouraged by the finding of Spassov *et al.*[4] that oxidation of amidrazone hydrazones (**4**) resulted in the formation of the corresponding triazoles. This suggests that these hydrazones exhibit ring-chain tautomerism and that the ring closed tautomers are subject to oxidation. In view of this, we reasoned that it might be possible to selectively trap the less stable but more nucleophilic triazolines (**7**) with α,α,α-trifluoro-*p*-tolyl isocyanate.[5]

As outlined in Scheme 2, the amidrazone hydrazones of formula (**6**) were readily obtained from *N*-(4-chlorophenyl)-4-chlorobenzenecarbohydrazonamide (**5**)[6] by condensation with the appropriate aldehyde or ketone in ethanol at ambient temperature. Hydrazones (**6c-6g**) crystallized from 0.15

molar reaction mixtures in 73-81 % yield while compounds (**6a**) and (**6b**) were obtained in an impure form by removal of the solvent under reduced pressure. ^{1}H Nmr analysis of compounds (**6a-6g**) (Table) in $CDCl_3$ indicated that these amidrazone hydrazones exist primarily in a single isomeric form. In addition, detectable amounts of the triazolines of formula (**7**) did not appear to be present in compounds (**6c-6g**). In the case of compounds (**6a**) and (**6b**) the major component was clearly the amidrazone hydrazone; however, since these materials were not further purified, the presence of the tautomeric triazolines (**7a** and **7b**) could not be ruled out.[7] These results are consistent with the finding of Spassov *et al.*[4] that the condensation of N^3-phenylarylamidrazones (**3**) with aryl aldehydes gives the open chain hydrazones.

Scheme 2



Treatment of hydrazones (**6**) with α,α,α-trifluoro-*p*-tolyl isocyanate in methylene chloride at room temperature resulted in slow conversion to less polar materials which were highly fluorescent under uv light. Complete reaction generally required about 24 hours (when R^1 was H or methyl) or heating at 55-60°C in 2:3 methylene chloride:1,2-dichloroethane for 1 to 3 days (when R^1 was aryl). The products were isolated in 33-84 % yield by removal of the solvent followed by crystallization from 1-chlorobutane (**8a** and **8c**) or 10% ethyl acetate in hexane. The ^1H nmr spectra of these products were consistent for 3,4-diaryl-4,5-dihydro-1*H*-1,2,4-triazole-1-carboxamides of formula (**8**). These

Table[a]

			Compounds 6			Compounds 8		
	R^1	R^2	mp(°C)	δ *pro*-C5-H	δ *pro*-C5-CH_3	mp(°C)	δC5-H	δC5-CH_3
a	H	H	foam	6.94 (d,1H) 7.61 (d,1H) J = 13.9 Hz	—	198-203[b]	5.70 (s,2H)	—
b	CH_3	H	gum	7.99 (q,1H) J = 5.4 Hz	2.08 (d, 3H) J = 5.4 Hz	180-184[c]	6.00 (q,1H) J = 5.4 Hz	1.68 (d,3H) J = 5.4 Hz
c	CH_3	CH_3	154-155	—	2.02 (s,3H) 2.12 (s,3H)	189-191	—	1.82 (s,6H)
d	Ph	H	114-115	8.62 (s,1H)	—	162-164	6.68 (s,1H)	—
e	4-ClPh	H	202-205	8.60 (s,1H)	—	207-209	6.65 (s,1H)	—
f	4-(OCH_3)Ph	H	171-174	8.57 (s,1H)	—	119-121	6.64 (s,1H)	—
g	4-(CN)Ph	H	210-214	8.60 (s,1H)	—	223-225	6.60 (s,1H)	—

[a] ^1H Nmr spectra were obtained in $CDCl_3$ at either 100 or 200 MHz.

[b] Purified by medium pressure liquid chromatography eluting with 10% ethyl acetate in hexane.

[c] Recrystallized from ethyl acetate.

assignments were based primarily on the chemical shifts of the substituents at C5 of the triazoline ring (Table). The differences in chemical shifts observed between compounds (**6**) and (**8**) are consistent with those observed in similar ring-chain tautomeric systems.[8] Products resulting from acylation of the open chain tautomer at N^2 or N^4 were ruled out on the basis of the ^1H nmr spectra.[9] In summary, a facile synthesis of 3,4-diaryl-4,5-dihydro-1*H*-1,2,4-triazole-1-carboxamides has been developed. Although our studies were focused on the use of 4-trifluoromethylphenyl isocyanate as the triazoline trapping agent, it should be possible to employ other isocyanates and similar electrophiles.

REFERENCES AND NOTES

† Dedicated to Professor E. C. Taylor on the occasion of his seventieth birthday.

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5. A similar strategy has been employed to convert aldehyde and ketone S-methylisothiosemicarbazones to 1,4-diacetyl-3-methylthio-4,5-dihydro-1*H*-1,2,4-triazoles by treatment with acetic anhydride. S. Kubota, *Chem. Pharm. Bull.*, 1988, **36**, 96.
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7. Compounds (**6a**) and (**6b**) were not storage stable at room temperature and were employed without further purification.
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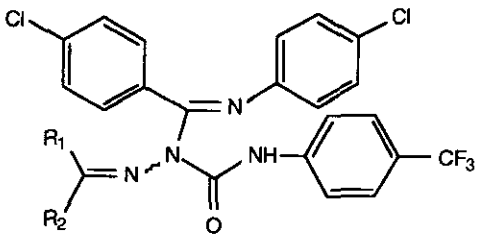
9. The products of acylation at N^2 or N^4, compounds (**9**) and (**10**) respectively, would display nmr

spectra consistent for hydrazones. In particular, the chemical shifts and multiplicities observed for the hydrogens and/or methyl groups at *pro*-C5 would be similar to those of compounds of formula (6).



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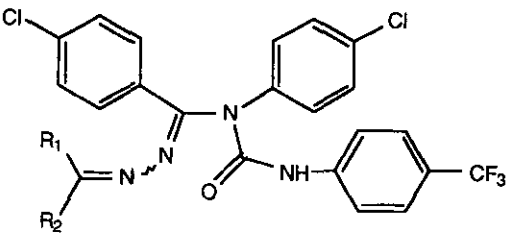

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